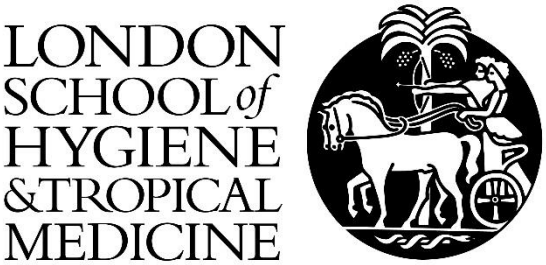

An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

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Abstract

As of 2016, women make up the majority of people living with HIV globally, and especially in sub-Saharan Africa where women and girls make up 59% of all people living with HIV. Female sex workers (FSWs) are at even higher risk of acquiring HIV, given vulnerabilities in criminalization of their work and challenges in negotiating safer sex. HIV prevalence among FSWs in South Africa is higher than any other sub-population, with a recent study recording a prevalence of up to 72% in the greater Johannesburg area, and 40% and 54% prevalence in Cape Town and Durban respectively.

To date, female-initiated HIV prevention options have been limited, with most interventions focused on male condom use. However, in the last few years, oral pre-exposure prophylaxis (PrEP) has been shown to be highly efficacious in preventing HIV infection among men and women, if taken consistently. To examine whether women, especially those who are considered part of key populations, will take up and use PrEP outside of clinical trials, many demonstration or pilot studies are underway around the world.

This thesis explores the real-world applicability and acceptability of oral PrEP in order to inform intervention design, implementation, and product use for female sex workers in South Africa. A range of methods were used to answer this overarching aim including:

- an adapted meta-ethnography to explore and understand previous research regarding motivations and barriers to uptake and use of female-initiated HIV prevention technologies that could be used by women in sub-Saharan Africa;
- formative research in South Africa, using a grounded approach to examine the practical and contextual factors that might influence successful delivery of a PrEP intervention with the aim of designing an intervention;
- focus group discussions with FSWs to examine community-level acceptability of PrEP with potential end users (the final activity in the formative research);
- demographic and behaviour surveys conducted during the Treatment And Prevention for Sex workers (TAPS) Demonstration Project to identify key characteristics of FSWs who took up and used PrEP within the context of TAPS; and,
- in the individual perspectives and lived experiences of PrEP users in TAPS are explored through analysis of in-depth face-to-face interviews with FSW.

The overall findings of this thesis point to the multi-dimensional aspects of individual needs, community perceptions and beliefs, clinic delivery platform and feasibility, as well as societal norms and environmental context which determine the ability of FSWs to successfully use PrEP. Recommendations for including and acknowledging these dimensions, as well as how to leverage them to develop more effective programmes are included.

Declaration

I, Robyn Eakle, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis document.

Signed: 

5 October 2017

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There are more people to thank for their support in the production of this PhD than space to write. First and foremost is my main PhD supervisor, Dr. Adam Bourne. No words can do justice in describing the support that Adam provided to me during the course of the monster that was this PhD, but I will try. Adam was a rock, a source of pragmatic rationalism when I felt like giving up, and my writing guru without whom none of these words would have made it on to a page. He was an amazing supervisor, always professional and supportive and pushed me to think beyond what I thought were my limits, but also a friend when I needed one.

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partner in getting the TAPS project done, from end to end, and there is no way we would have gotten the main paper out so quickly without her unbelievable dedication and determination. I have learned so much from her and will always cherish our late-night, wine-filled working dinners, and of course, her friendship.

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To my friends far and wide who have been there, given me a home when I needed it even for a short period of time, and sometimes quite literally saving my life – I may not even be here if it wasn't for you. Holly and Lizzie, Michelle, Paul, Stephanie, Kenny, and Ellie, I will be eternally grateful.

Finally, I thank my family who have supported me, mostly from afar, over the course of the past few years and have put up with my long absences. Your support has meant so much.

Statement on Personal Role in this Research

The majority of the research described in this PhD was imbedded in the TAPS Demonstration Project. I am Co-Principal Investigator for the project, as well as the overall project lead. I designed the project with the three other Investigators (Dr. Gabriela Gomez, Prof Francois Venter, and Prof Helen Rees); led the formative research; led the writing of protocols and all ethics and regulatory applications; led most of the research tool design; hired and managed the entire project team; and managed the day to day operations of the study. Although the manuscripts contained within this PhD are co-authored with others, I was the lead for all of the manuscripts. I also led the analysis on all papers, except for the TAPS project results paper for which the statistical analysis was led by Dr. Gabriela Gomez supported by myself.

Dissemination of PhD related data

Data from this PhD and the TAPS Demonstration project have been disseminated at a number of conferences in the form of posters and oral presentations, as well as published journal articles. Dissemination details are as follows:

- Poster at AIDS 2014 in Melbourne on meta-ethnography
    - **Eakle R**, Jarrett C, Bourne A, Rees H, Larson HJ. What works for women? Understanding the motivations and barriers to uptake and use of female-initiated HIV prevention technologies in Sub-Saharan Africa. AIDS Conference. Melbourne, Australia. TUPE122. 2014
- Meta-ethnography protocol published in 2015
    - **Eakle R**, Jarrett C, Bourne A, Stadler J, Larson H. Protocol for a systematic review: understanding the motivations and barriers to uptake and use of female-initiated, primary biomedical HIV prevention technologies in sub-Saharan Africa. Systematic Reviews. 2015 Aug 19;4(1):111.
- Poster at R4P 2014 in Cape Town on TAPS Design
    - **Eakle R**, Gomez G, Venter WDF, Rees H. Expanded Use of Antiretrovirals (ART) for Treatment and Prevention for Female Sex Workers in South Africa. R4P Conference. Cape Town, South Africa; 2014
- TAPS protocol published in 2016
    - Gabriela B Gomez‡, **Robyn Eakle***‡, Godspower Akpomiemie, Judie Mbogua, W D Francois Venter, Helen Rees. Treatment And Prevention for female Sex workers in South Africa: protocol for the TAPS Demonstration Project. BMJ Open. 2016.
- Poster at R4P 2014 in Cape Town on focus group discussions
    - **Eakle R**, Manthata G, Stadler J, Mbogua J, Sibanyoni M, Venter WDF, et al. Preparing for PrEP & Immediate Treatment: Focus Group Discussions in Advance of a Demonstration Project in South Africa. R4P Conference. Cape Town, South Africa; 2014
- Oral presentation and poster at R4P 2016 in Chicago on interim TAPS results
    - **Robyn Eakle**, Gabriela B Gomez, Niven Naicker, Judie Mbogua, Rutendo Bothma, Michelle Moorhouse, W D Francois Venter, Helen Rees. Treatment And Prevention for female Sex workers in South Africa: interim results for the TAPS Demonstration Project. R4P Conference. Chicago, IL. USA. 2016.

Data from this PhD and the TAPS project have also supported a number of other demonstration projects, as well as meetings, trainings, and PrEP guideline development including:

- PrEP demonstration project in Benin for female sex workers conducted by University of Manitoba and local department of health;
- PrEP demonstration project conducted for female sex workers by Médecins sans Frontières in Mozambique;
- PrEP Guidelines Meeting, UNAIDS/WHO, March 2015;
- South African National Guidelines on PrEP and test and treat for sex workers;
- Clinical and implementation training curricula on PrEP for South African National Department of Health and Southern African Clinicians Society; and,
- Presentation at the Office of the Global AIDS Coordinator (OGAC)/PEPFAR, April 2016 in support of PrEP rollout.

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List of Tables and Figures

List of Abbreviations

3TC	Lamivudine
ADAPT	Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking
ANC	Antenatal Care
ART	Antiretroviral therapy
ARVs	Antiretrovirals
AVAC	Global Advocacy for HIV Prevention
CAB	Community Advisory Board
CBD	Central Business District
CD4	Cluster of Differentiation 4
CDC	United States Centers for Disease Control
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DoH	Department of Health
EFV	Efavirenz
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FEMPrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FGDs	Focus Group Discussions
FSWs	Female Sex Workers
FTC	Emtricitabine
GCP	Good Clinical Practice
GPP	Good Participatory Practice
HCT	HIV Counselling and Testing
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSRC	Human Sciences Research Council
HREC	Wits Human Research Ethics Committee
HTS	HIV Testing Services
IDIs	In-depth interviews
ITx	Immediate Treatment
JHB	Johannesburg
LQR	Longitudinal Qualitative Research
LSHTM	London School of Hygiene & Tropical Medicine

MAMA	also MomConnect
MCC	Medicines Control Council
MDR-TB	Multi-drug resistant tuberculosis
MEMS	Medication Event Monitoring System
mHealth	Mobile Health (technology)
mL/min	Millilitre per minute
MSEM	Modified social ecological model
MSM	Men who have sex with men
NDoH	National Department of Health
NiMART	Nurse-initiated and Managed Antiretroviral Treatment
NSP	National Strategic Plan on HIV, STIs and TB
PEP	Post-exposure prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief
PICT	Provider Initiated Counselling and Testing
PMTCT	Prevention of Mother to Child Transmission
PPTS	Participants
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International database of prospectively registered systematic reviews in health and social care
PROUD	Pre-exposure Option for reducing HIV in the UK: immediate or Deferred
PTA	Pretoria
RNA	Ribonucleic Acid
SAHMS	The South African National Health Monitoring Study
SANAC	South African National AIDS Council
SD	Standard Deviation
SMS	Short Message System
STIs	Sexually Transmitted Infections
STRIVE	Programme on Tackling the **Str**uctural Dr**ive**rs of HIV
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
SWOP	Sex Worker Outreach Project
SWP	Sex Worker Programme
TAPS	**T**reatment **A**nd **P**revention for female **S**ex workers
TB	Tuberculosis
TDF	Tenofovir

TOP	Termination of Pregnancy
USD	United States Dollar
UNAIDS	Joint United Nations Programme on HIV and AIDS
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute

1.0 General Introduction

1.1 Overview

This general introduction chapter provides the background, history, rationale and conceptual basis for this PhD research. The chapter is broken down into sections that examine:

- the HIV epidemic;
- the nature, definition, and importance of sex workers as a key population in relation to the HIV epidemic;
- HIV prevention options for women;
- ARV-based prevention and the product development pipeline;
- the case for oral PrEP, in particular for sex workers;
- the call for implementation research and the TAPS Demonstration Project providing the context for this PhD; and,
- an outline of the PhD aims and objectives, underlying framework, and thesis structure.

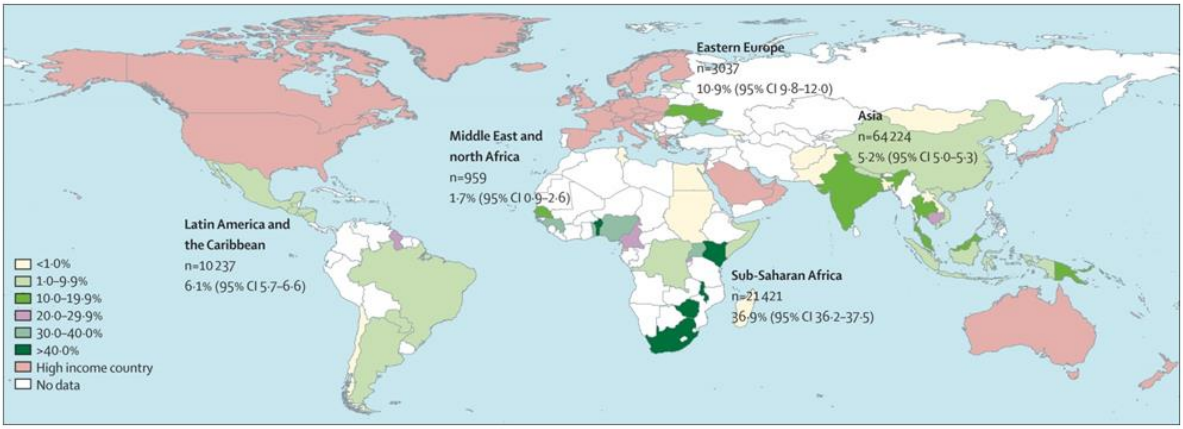
It is important to note that this PhD thesis has been prepared in a publication style. A total of six papers are presented throughout Chapters 2 - 6 which speak to the overarching aims and objectives, outlined in Section 1.11. In order to avoid repetition, certain issues are briefly introduced in the context of this introduction to help provide a clear rationale for the overall study, but are explored in more detail in the introduction sections of the papers that follow in later chapters.

1.2 The public health problem

The most recent World AIDS Day Report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) highlighted that the decline in the global rate of new HIV infections has stalled, and that key populations including young women (YW), people who inject drugs (PWID), sex workers (SWs), men who have sex with men (MSM), and transgender people still remain at highest risk (1). Additionally, women in general are disproportionately affected by HIV due to both biological and social factors (2), although biological susceptibility is not yet fully understood (3,4). Issues of social and gender inequality, particularly in situations where gender-based violence is present, have been shown to increase a woman's risk of HIV (5).

Female sex workers (FSWs) experience even higher rates of HIV and, at a global level, are 10-13.5 times more likely to be living with HIV than other women (1,6). The most recent pooled analysis of FSWs in sub-Saharan Africa found the HIV prevalence rate to be 36.9% (7). Attempts have been made to estimate the size of sex worker populations globally and regionally, however this has proven to be a difficult undertaking since many countries have not conducted focused mapping exercises, and in those that have, counting strategies vary considerably (8,9). Additionally, sex worker populations can be highly mobile, and many women who sell sex do not actually consider themselves to be sex workers making them even more difficult to identify and assess their risks (10).

Figure 1. Prevalence of HIV in FSWs by region (6).



1.3 Definition of Sex Worker

Given the varied nature of sex work, it is important to define here the term 'sex worker' as it is used throughout this PhD. In 2012, UNAIDS defined sex work as:

> *"female, male, and transgender adults and young people (18 years of age and above) who receive money or goods in exchange for sexual services, either regularly or occasionally."*(11)

This definition combines the notion of formalised sex work, in which a person may identify themselves as a sex worker and accept money or other goods in exchange for services, as well as transactional sex, which is defined by a less formalised interaction where sexual favours are exchanged for some type of material gain, while the person may not identify themselves as a sex worker. Specific definitions for transactional sex continue to evolve as more nuanced understanding of the interaction develops (12). The dynamics of HIV transmission are likely to be very different between those identifying as 'sex workers' and those engaging in

transactional sex, and HIV prevention programming often distinguishes the two for the purpose of targeting interventions.

The definition of sex work utilised in the current research, draws on the formalised constructs reflected in the UNAIDS definition of 2000:

> *''any agreement between two or more persons in which the objective is exclusively limited to the sexual act and ends with that and which involves preliminary negotiations for a price.''*(13)

This definition clearly excludes notions of love, relationships or security, limiting to services in exchange for money or what might constitute a price. This definition was chosen for this project in order to reflect the context in which the research was conducted, as it was imbedded within a larger study targeting interventions specifically for self-identified FSWs.

1.4 Sex Workers as a Key Population

Sex workers are defined as a key population since they are more likely to be exposed to HIV as part of their work, and may be more likely to engage in sex where onward transmission of HIV is possible, both with clients and regular partners. Indeed, in areas where education and empowerment programmes exist, sex workers report high rates of condom usage with clients (14), however, power and relationship dynamics, including trust, play a role in whether condoms are used with main or regular partners (15,16).

The ability to negotiate condom use and prevent HIV among female sex workers, as well as preserve overall safety on a day to day basis, has been shown to be dependent on several factors (10,17): age and length of time in sex work as well as sex work locale (brothel or hotel, versus street based); structural issues related to criminalisation (whether police use the discovery of condoms to single out and arrest sex workers for instance), violence, substance use, and poverty (whether condomless sex is considered at premium prices) (18–23). A systematic review of alcohol use and risky sexual behaviour in populations in sub-Saharan Africa showed that alcohol use directly correlated to lower rates of condom use (21). Another systematic review found that sex workers had a lifetime prevalence of any type of violence of 45-75%, and 32-55% in the last year (19), which is also directly correlated to acquisition of HIV. This violence comes from a variety of sources including clients, pimps and other operators in the sex work trade, intimate partners, police, and community members who do not support the trade.

For these reasons, sex workers are considered a highly vulnerable population, and have been the focus of many efforts worldwide to try to remove, or at least reduce, some of these vulnerabilities (13,24–27). These efforts have in turn promoted national and local strategies to focus on improving specific contexts.

1.5 Sex workers in South Africa

In South Africa, the HIV epidemic continues to be one of the largest in the world, making up nearly half of the HIV burden in sub-Saharan Africa (1). The most recent Human Sciences Research Council (HSRC) HIV Prevalence, Incidence, and Behaviour Survey revealed an overall national HIV prevalence in women of 14.4%, with rates as high as 17.4% to 31.6% between the ages of 20 and 49, a segment of the population considered to be significant in driving the epidemic (28).

The HIV prevalence among FSWs in South Africa was estimated to be between 44-69%, with 19.8% of all new infections in South Africa originating from FSWs, their regular partners, and their clients (29,30). However, figures published more recently found a prevalence of 72% in the greater Johannesburg area, and 40% and 54% in Cape Town and Durban respectively (31). A report from the South African National AIDS Council (SANAC) estimated that sex workers make up 1.1% of the adult population in South Africa (132,000-182,000), with women comprising 91% of the sex worker population (32).

The high prevalence of HIV among FSWs in South Africa, in combination with the many vulnerabilities inherently faced by sex worker populations in general, led to the development of a national sex worker plan by SANAC, highlighting sex workers as a priority population for tailored prevention and HIV treatment services (33). This plan is in the process of being implemented throughout all South African provinces in a number of sex worker specific clinics. In addition, interventions and policies targeting sex workers have also been prioritised in the former and most recent National Strategic Plans for HIV, Tuberculosis (TB), and Sexually Transmitted Infections (STIs) where the need for more HIV prevention options, especially for vulnerable populations, has been underscored (34,35). These plans are also linked to the sex worker specific plan (33).

1.6 HIV prevention options for women

There have been limited choices for women in terms of HIV prevention methods, in spite of continued product and implementation development research to broaden the method mix. The use of male condoms, while efficacious in preventing HIV, heavily depends on the willingness of men to use them (36), therefore protection from HIV through the use of male condoms is dependent upon a woman's ability to negotiate use (37).

The female condom is a female-initiated HIV prevention option, but its accessibility has been variable at best (38). A report in 2009 from the Global Campaign for Microbicides cited that in 2005 13.9 million female condoms were available for use, while somewhere between 6-9 billion male condoms were available (39). More recently, efforts have focused on promoting female condom distribution in certain countries and globally (40–42).

Additionally, there has been limited availability of post-exposure prophylaxis (PEP), a method in which antiretrovirals (drugs which target and treat retroviruses such as HIV - ARVs) are administered for a 28-day period to prevent HIV seroconversion following suspected exposure (43). PEP has been predominantly programmed for post-rape care or occupational exposure (44,45) in low and middle income countries, largely due to social biases against providing the medication for unexpected sexual exposure outside of rape. The World Health Organization (WHO) guidelines, however, recommend broader uses for PEP to cover more general, episodic cases of suspected exposure resulting from unprotected sex (46,47).

The effect of these social and logistical circumstances is that, until very recently, there have been only two female-initiated prevention options: PEP and the female condom. Their limited availability and uptake, combined with the sustained rates of HIV among women, have demonstrated a clear need to provide more female-initiated and controlled technologies.

1.7 ARV-based prevention and the prevention product pipeline

To broaden the HIV prevention method mix, there have been wide-scale, concerted research efforts to expand the use of ARVs for prevention purposes (48). Following PEP and the ARV-based prevention of mother to child transmission (PMTCT)(48), focus initially turned to developing a topical, or vaginally-based, female controlled product to prevent HIV (49,50). Products took the shape of vaginally applied microbicide gels, much like lubricants but requiring larger quantities to be applied. Unfortunately, most of these products showed a range from no to little efficacy, and in some cases, even harm (51–58). These studies did,

however, pave the way for further research and provided valuable knowledge around acceptability of such products. From these studies, the nuanced dimensions of acceptability including personal, social, political, and environmental, were illuminated from research which initially had focussed only on product attributes (59). These nuances are explored further in both Chapters 2 and 4.

One other female initiated product, the diaphragm, was tested for protection against HIV but did not prove effective in preventing acquisition. Biological reasons are now known to be attributable to the failure of these, as diaphragms do not provide enough of a barrier to cover all vaginal tissues which may be exposed to HIV. With regards to the gel, and other ARV-based products, it has been shown that high drug concentrations in the vaginal tissues of a given product are needed in order to confer protection (60). This issue combined with the problems with adherence to the daily gel regimens, have made for ineffective products to protect against HIV.

Given the high efficacy of PEP and PMTCT, options for oral pre-exposure prophylaxis (PrEP – described further in the following section) became part of the product development pipeline. The first study, iPrEX, was conducted among men who have sex with men (MSM) which found an initial low level of efficacy at 44% (61), however further analyses of high adherence sub-groups found much higher rates of protection up to 90% compared to placebo (62). This same sub-study found that with perfect seven-day dosing, protection could be as high as 99% among MSM.

Additional PrEP studies followed in several countries and among a variety of populations, including serodiscordant couples and high-risk women. Results from these studies further confirmed the efficacy of PrEP among those people who took the drugs regularly (63). However, the two studies conducted exclusively among high risk women did not show efficacy of the intervention due to lack of adherence (64,65), pointing to the need for further research around risk assessment and implementation.

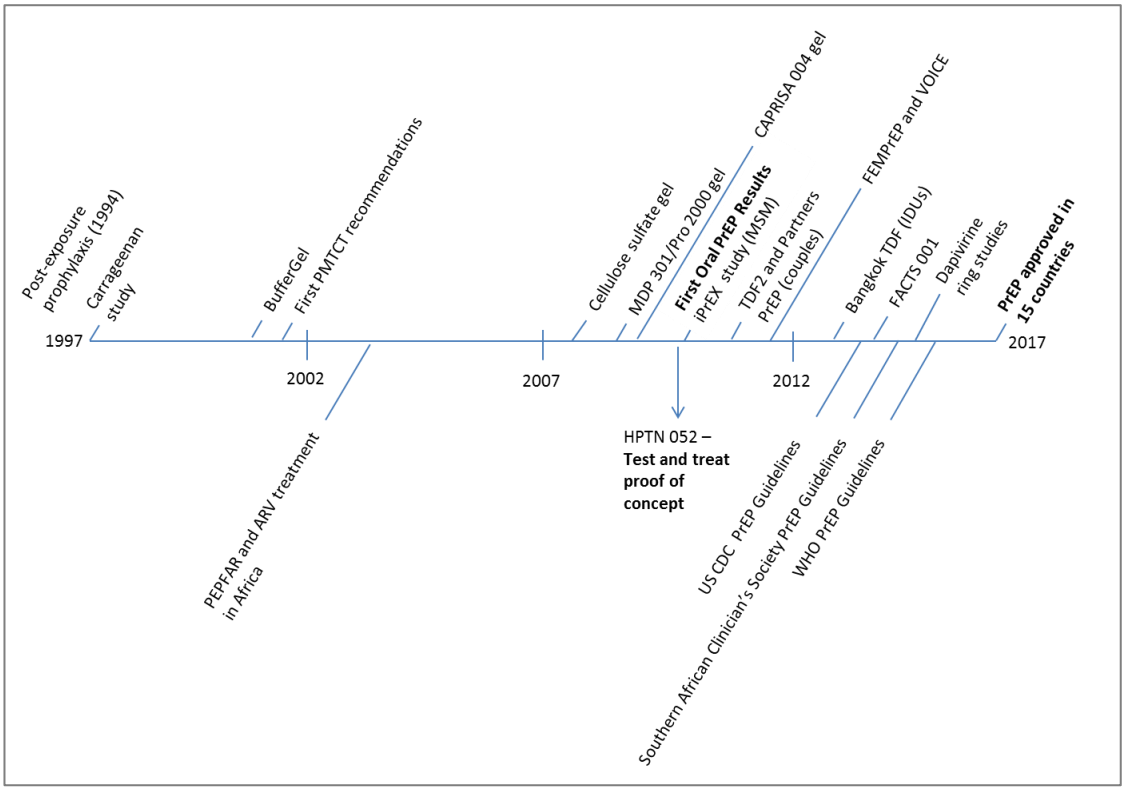
Concurrently, clinical trials also investigated the provision of antiretroviral treatment as soon as someone has an HIV-positive test, rather than waiting for their CD4 count to drop below a certain level as had previously been the case in most countries. This approach, now termed ‘test and treat’ in most guidelines, has been found to reduce onward transmission of HIV and has produced better health outcomes (66,67). As a result, the standard of care recommended

by the World Health Organization (WHO) in 2016 now includes PrEP as an HIV prevention option and the test and treat approach (68).

Studies to further expand the method mix continue, with recent results from the vaginal dapivirine ring (ARV-based) product trials with more promising, though still moderate results (37% and 31% efficacy in protecting against HIV acquisition in the two phase III studies) (69,70). The ring and other new and previously tested prevention options are providing the basis for further research into future stand-alone and multi-purpose technologies. Because of the significant behaviour requirements to maintain consistent pill taking in the case of oral PrEP, additional options for modes of preventive ARV delivery are in development. These include injectables, vaginal rings and films, and co-formulated products (for contraception, STIs, and HIV prevention), which are postulated to promote better uptake as people are able to make choices which fit best with their lifestyles (71–73).

The history of ARV-based product development is illustrated in Figure 2 which shows more than 20 years of research consisting of a multitude of studies with dates of results, as well as when guidelines were released.

Figure 2. An illustration of the last 20 year of ARV-based prevention product development



Note: Dates and products represent results unless otherwise noted. Data for this timeline were extracted from several sources (51,54,55,74,75).

1.8 The case for Oral PrEP

The oral PrEP regimen, as recommended by current guidelines (WHO, US Centers for Disease Control (CDC), and South Africa), entails taking a daily ARV, dual-drug combination pill (tenofovir and emtricitabine) and requires three monthly HIV testing to confirm continued HIV-negative status in PrEP users (68,76,77). Due to this rigorous commitment, it is hypothesized that highly motivated populations, e.g. those at self-recognised higher risk, will be better candidates for PrEP than the general population (78). In this context, highly motivated populations may be defined as people in higher risk environments who also recognise their own risk, such as sex workers (22,27,79). Modelling studies have also shown that targeting high HIV incidence populations, even in generalised epidemics, such as sex workers or MSM should be prioritised where PrEP is likely to have the greatest impact, especially in generalised epidemics (80,81). Estimations of impact, however, are directly related to the HIV prevention and treatment programming context within a country. For instance, South Africa and Swaziland have shown success in the secondary prevention benefits of scaled-up ART programmes, reducing new infections by treating HIV-infected people thereby preventing onward transmission (82,83). However, even in these countries, it has been acknowledged by policy makers that HIV treatment must go hand in hand with all available HIV prevention options in order to fully control the epidemic (84,85).

Interestingly, despite the considerable interest in preventing and treating HIV among sex work populations, very few models have been developed specifically for sex workers to examine the potential impact of PrEP. Those which have been developed have focused on the FSW population in Hillbrow, an inner-city district of Johannesburg, South Africa, as well as for the Avahan project in India (86,87). These models mostly explored the impact and cost-effectiveness of vaginal microbicides within the context of STIs and prevention programming, however some models are now being adapted to explore strategic PrEP programming.

Although it has been shown that PrEP can significantly reduce the risk of acquiring HIV, its development and implementation has been a significant source of debate. Concerns have included risk of generating additional resistance to ARVs, the potential for behavioural disinhibition, the potential for pill sharing or selling, the difficulty of delivery, ethics relating to supply and distribution of ARVs, and cost (88,89). These concerns have been voiced over time in an evolving fashion by certain groups of advocates, researchers, and policy makers, though these opinions continue to change as new evidence has emerged.

PrEP represents a new option for HIV prevention which may give key populations such as FSWs an opportunity to protect themselves beyond male and female condoms, or PEP. PrEP also relies on the person taking it, and while external factors may influence use, PrEP use does not necessarily require negotiation, as compared with male condoms for instance. In addition, PrEP can provide added protection in addition to condoms such as for the uninfected partner in a serodiscordant couple, or for women who experience repeated episodes of sexual violence. However, there has been very little concerted research among FSW populations regarding PrEP use. Some of the efficacy studies, such as FEMPrEP and VOICE (64,65), targeted women at high risk which inherently included sex workers, however they were not the focus of the research.

The ability to practically deliver PrEP, in particular among key populations, has been the largest open question, both in terms of whether people would take it consistently enough to benefit from its protection and in terms of cost-effectiveness. The two PrEP efficacy trials including only women and demonstrating lack of efficacy, failed largely due to issues with low adherence (64,65). However, the qualitative research published following the VOICE and FEMPrEP studies revealed highly nuanced reasons for lack of use, including: misconceptions about personal risk, logistical issues attending the clinic, apathy towards research, and asserted lack of interest in the product but intense interest in the high quality health services provided by the clinical trial clinics, which were otherwise scarce or completely unavailable through existing community services (90,91). Some questioned whether oral PrEP would ever be a viable product for women who, in large numbers in these studies, demonstrated little interest in consistent PrEP use (92–96). However, it was generally agreed that in the absence of many prevention choices, the product should be made available following additional research into the nuanced feedback received from the trials and previous prevention efforts.

1.9 Acceptability, applicability, and the role of Implementation Science

In light of the PrEP adherence issues, as well as the fact that PrEP represented a completely new modality of HIV prevention, there was a clear need for implementation research in order to develop best practices for successful delivery. As a result, and as a first step in this direction, the WHO called for demonstration projects to be conducted in advance of country programming in order to inform their eventual normative guidelines (97). This call, along with financial support from funders, pushed implementers to explore not only the mechanics of delivering PrEP (e.g. the logistics of which clinics, in which settings, using which supply chain

mechanisms, levels of staff needed, and cost), but also the qualitative perspectives of providers (98–101) as well as potential users (102,103), the latter of which has provided the basis for this PhD thesis. To date, this research has been focused largely within in the context of PrEP provision for MSM as this population was among the first to have access, in particular in more developed contexts.

The principle or discipline of Implementation Science is defined by the Fogarty International Center at the United States National Institutes of Health (NIH) as:

> *"the study of methods to promote the adoption and integration of evidence-based practices, interventions and policies into routine health care and public health settings. Implementation research plays an important role in identifying barriers to, and enablers of, effective global health programming and policymaking, and leveraging that knowledge to develop evidence-based innovations in effective delivery approaches."*

The success of rolling out a new intervention, or improving existing ones, is dependent upon many things: political support from stakeholders including all levels of the health sector, education and support of providers, capacity of the health system including clinics and the supply chain, and strategic messaging for health promotion and communication. These are all overarching, structural aspects of the feasibility of intervention delivery that are critical to ensuring success.

In terms of the research presented in this PhD, however, exploration of feasibility was included as it related to the design of the PrEP intervention, and in relation to the applicability and acceptability of PrEP for FSWs. Specifically, applicability as used throughout this PhD, refers to the relevance and responsiveness of the intervention to fill the needs of the women taking it up from more of an external, implementer perspective (or top-down). Acceptability, intrinsically linked to applicability, concerns a more internal user-centred (or emic (59)) perspective (or bottom-up) of whether a product 'fits' within their lives, fills a gap or makes a valuable addition. It also explores the meaning of the product or intervention to the user. These two aspects also exist at the core of Implementation Science efforts.

Many strategies in the HIV/AIDS response have centred on top down approaches. For instance, some campaigns have focused on the dynamics of virus transmission for the purposes of policy making and national programming, such as "Know Your Epidemic, Know Your Response" (104).

At the surface, Implementation Science, lays out a process for studying and evaluating implementation of interventions usually dictating the importance of incorporating policy makers and providers into the development and dissemination of intervention programming and often employing a top down approach (105,106). Programme Science is another similar, evolving approach, which further delineates specific spheres of knowledge and practice to achieve certain outcomes (107). While widely popular for designing intervention programming strategies, these approaches do not explicitly seek out the input and perspectives of the target population on intervention design.

Schools of thought, such as the Diffusion of Innovations Theory, underscore the importance of including the target population during the conception of product and intervention design (108). This theory poses a process by which a new idea or innovation is taken up by a population or culture and incorporated into practice. The theory dictates that diffusion requires four elements: innovation, communication channels, time, and a social system. It is heavily dependent on the people within the social system. One of the core tenants of the theory is that the innovation must grow out of a specific need of the target population, and solve a perceived problem. Thus, understanding which problem an innovation solves and for which people, is as important as understanding how the innovation will be disseminated.

The PrEP efficacy trials demonstrated that the product will prevent acquisition of HIV if taken correctly, but some individuals may not want to take a daily pill to prevent HIV, as suggested in the failed trials in women. Strategies for promoting and measuring adherence were not clearly understood as they related to the context of the study populations (109). However, as a new HIV prevention technology, PrEP represents an opportunity to build an in-depth understanding of whether it will be taken up and used, by whom, how, and why. To accomplish this task, it is necessary to engage the target population during the demonstration project stage to identify individuals who want to use PrEP and explore their perspectives. This engagement will help to develop an understanding of why the intervention may succeed or fail and can produce evidence that can be used in scale-up to implement PrEP in a way which is applicable (relevant and responsive) to their lives.

In this spirit, Implementation Science plays a key role as the principle underpinning the research described throughout this PhD, in conjunction with the social ecological model further described in Section 1.11.3.

1.10 The TAPS Demonstration Project

In response to the call for PrEP implementation research, the Treatment And Prevention for Sex workers (TAPS) Demonstration Project was designed and implemented in South Africa to assess the deliverability of PrEP among FSWs. TAPS was led by the Wits Reproductive Health and HIV Institute (RHI) based in Johannesburg. The study offered oral PrEP to HIV-uninfected FSWs as well as early HIV treatment (ART)[1] to FSWs diagnosed with HIV (with a CD4 count outside of South African National Department of Health guidelines (NDoH)) in two urban sites in South Africa (Johannesburg and Pretoria) (110). The protocol for this study has been published in BMJ Open, and is included in Appendix xiii.

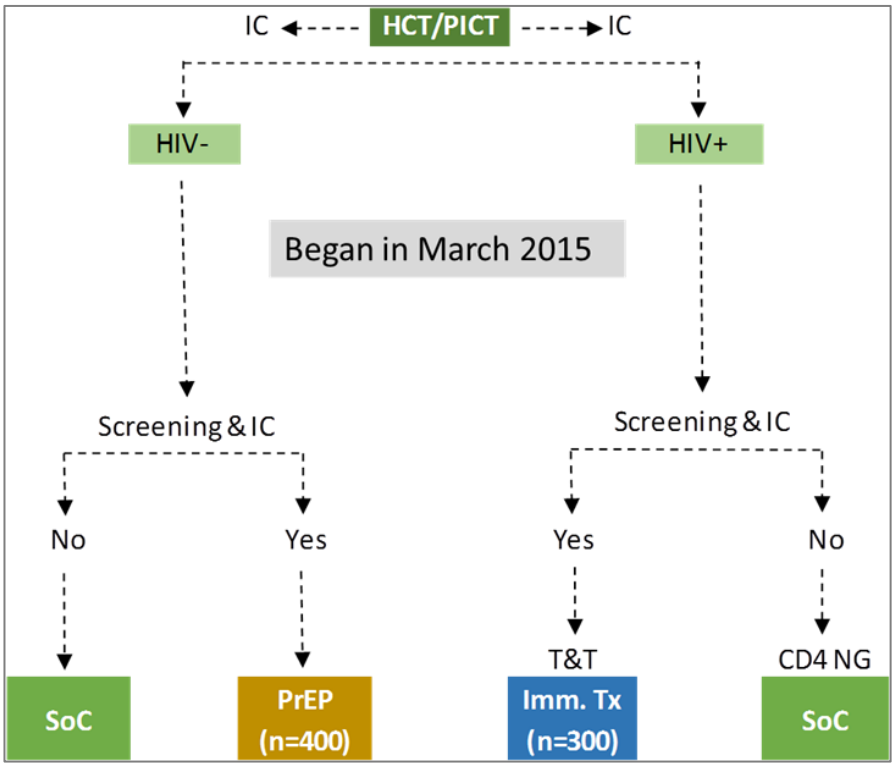
In summary, the success of the demonstration project was evaluated based on the primary outcome which was the number of FSWs retained in the study at 12 months, with secondary aims to monitor and assess several outcomes and service delivery factors including: uptake and adherence, retention over time (3, 6, 12, 18, and 24 months), pregnancy rates, safety, side effects, patterns of PrEP use, sexual behaviour change, and the use of SMS technology for adherence support and healthy living[2]. A large component of the study was the qualitative research which aimed to understand FSW participation in the project and use of the PrEP and early ART interventions. A costing study and economic evaluation paired with transmission modelling were also included to assess cost-effectiveness and impact.

No participation reimbursement was offered, except for the additional qualitative research which required selected participants to attend the clinic for in-depth interviews (IDIs). Participants were expected to be enrolled in the study for at least 12 months to meet the minimum follow-up time, however the study ran from March 2015 until July 2017. The study design and flow, as well as points at which data were collected for this PhD, are shown in Figures 3 and 4. Figure 5 is a timeline for the entire span of the TAPS project, also included for publication in the supplementary material (Figure S1) in the paper presented in Chapter 5.

[1] This was originally called immediate treatment in TAPS, but changed over time with evolving NDoH guidelines in South Africa. It was later termed early ART, but in the new national programme is now called test and treat in line with WHO and UNAIDS terminology.

[2] SMS reminders have been used in ARV treatment programmes to support adherence (111,112). This demonstration project incorporates them as a support mechanism for adherence and healthy living.

Figure 3. TAPS intervention screening and initiation flow



Abbreviations: HCT/PICT = HIV testing and counselling/provider initiated counselling and testing (per South African guidelines); IC = informed consent; SoC = standard of care; Imm. Tx = immediate treatment (early ART).

In Figure 4, red circles are drawn around where data were collected as part of this PhD project. Quantitative data for exploring characteristics of women taking up PrEP were collected in a baseline questionnaire just before enrolment. These data, along with the data collected in the design phase of TAPS (later described in Chapter 3) speak to the more formative elements of the research. The design phase is illustrated in Figure 5 as the formative research during which qualitative data were also collected through focus group discussions, and through in-depth interviews indicated in Figure 4. These data speak to the community and individual perspectives of acceptability from the user side.

Figure 4. Clinic and research flow of TAPS

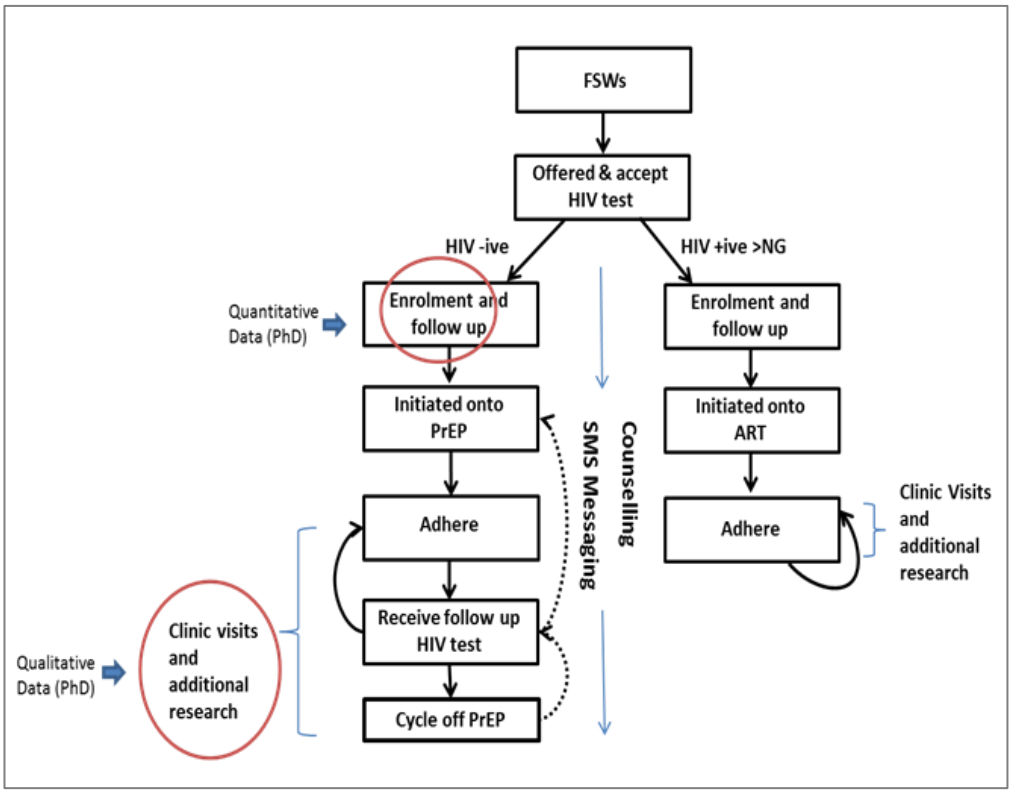
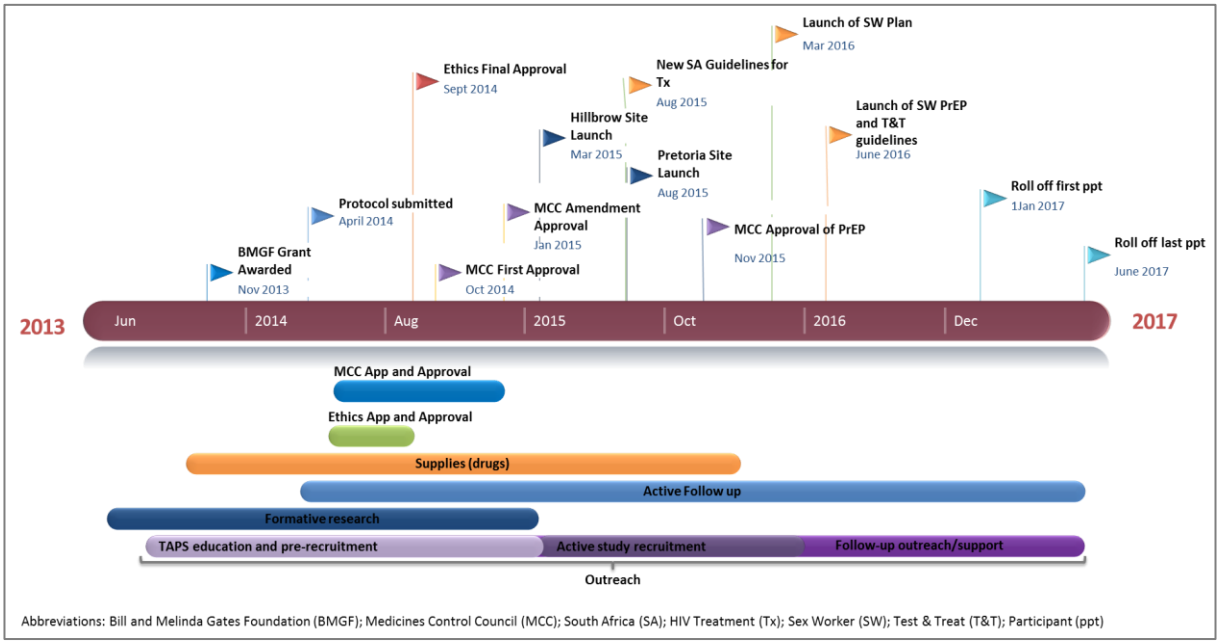


Figure 5. TAPS project timeline



1.11 PhD Research

As a key population identified by South African policy makers in the national strategic plans, FSWs in South Africa were a logical starting point for the implementation of PrEP as a new HIV prevention intervention. However, in order to design an appropriate intervention for delivery which addresses the needs of this target population, it was necessary to first develop foundational knowledge of experiences with past interventions. Following that, came the process of developing a holistic understanding of the women most suited and motivated to use PrEP within the FSW population, understand how it could fit into their lives in terms of applicability, and why they might take it up which speaks to the larger notion of acceptability. This became the overarching purpose of this PhD.

1.11.1. Primary Aim

This thesis explores the real-world applicability and acceptability of oral PrEP in order to inform intervention design, implementation, and product use for female sex workers in South Africa.

1.11.2. Objectives

1. Explore previous research regarding motivations and barriers to uptake and use of female-initiated HIV prevention technologies by women in sub-Saharan Africa.
2. Examine the practical and contextual factors that might influence successful design and implementation of a PrEP intervention for FSWs in South Africa.
3. Examine community-level acceptability of PrEP among FSWs.
4. Describe key demographic characteristics of FSWs who take up and use PrEP in South Africa.
5. Explore individual perspectives and lived experiences of female sex workers who take up and use PrEP in the TAPS Demonstration Project.

These objectives will be met via a diverse range of methods including: a systematic review, exploratory formative research, focus group discussions, descriptive review of quantitative cohort data, and in-depth interviews. These methods are described in detail in the subsequent chapters, however a brief summary (including how each method and analysis maps to each objective) is contained in Table 1.

Table 1. PhD Research Objectives, Methods/Analyses, and Papers

Objectives	Methods/Analysis	(Chapter) Papers/Aims
1. Explore previous research regarding motivations and barriers to uptake and use of female-initiated HIV prevention products by women in sub-Saharan Africa.	Systematic review and analysis in the form of an adapted meta-ethnography	**(2a) Protocol for a systematic review: understanding the motivations and barriers to uptake and use of female-initiated, primary biomedical HIV prevention products in sub-Saharan Africa.** Aim: This protocol describes in detail the methods developed and used to conduct an adapted meta-ethnography on the motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa.
		(2b) Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography Aim: The primary aim is to identify and understand the motivations and barriers affecting uptake and use of female-initiated, primary biomedical HIV prevention products for women in sub-Saharan Africa. Findings and recommendations will aim to inform future HIV prevention policy and programming for women.
2. Examine the practical and contextual factors that might influence successful design and implementation of a PrEP intervention for FSWs in South Africa.	Systematic, iterative formative research and analysis based on a grounded approach	**(3) Designing PrEP and early HIV treatment interventions for implementation among female sex workers in South Africa: developing and learning from a formative research process** Aim: This paper describes the detailed decision making and conduct of formative research undertaken to design two new HIV prevention and treatment interventions delivered to female sex workers in a demonstration project in South Africa.
3. Examine community-level acceptability of PrEP among FSWs.	Focus group discussions/thematic analysis	**(4) Exploring acceptability of oral PrEP prior to implementation among female sex workers in South Africa** Aim: This paper focuses on aspects of PrEP acceptability as a new intervention within the context of a larger service delivery programme including the simultaneous roll-out of early ART. The aim of this paper is to explore PrEP acceptability among the FGD participants as future potential users.
4. Describe key characteristics of FSWs who take up and use PrEP in South Africa.	Baseline survey/ descriptive analysis	**(5) Antiretrovirals for HIV treatment and prevention among female sex workers: results from a real-world demonstration project** Aim: This paper presents the final analysis of uptake, retention, and cost results, including characteristics of women taking up the interventions, adherence and clinical outcomes.
5. Explore individual perspectives and lived experiences of female sex workers who take up and use PrEP in the TAPS Demonstration Project.	In-depth interviews/thematic analysis	**(6) The PrEP Life: female sex workers' perspectives on uptake and use of daily pre-exposure prophylaxis for HIV prevention in South Africa** Aim: This paper will explore the experiences of taking up and using PrEP among FSWs engaged in TAPS.

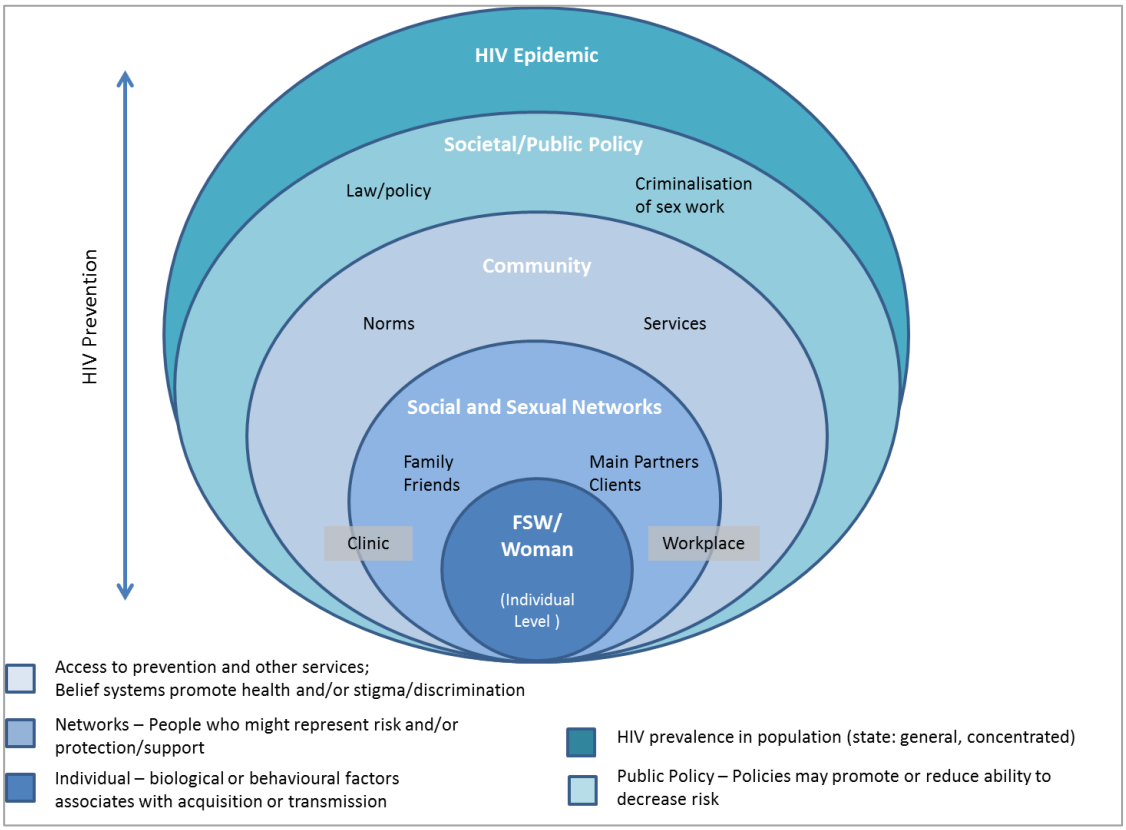
1.11.3. Underlying thesis framework: the Modified Social Ecological Model

Theoretical models and frameworks have been developed over the years to describe and understand a multitude of domains relating but not limited to behaviour, individual and social change, communication, networks, and decision making (90). Models and frameworks can also be used to organise research around a given topic. For this PhD project, a review of models and frameworks relating to the HIV epidemic, social dynamics, behaviour change and decision making was undertaken to devise a means of organizing the thought process and progression of the research.

Following the review, the Modified Social Ecological Model (MSEM) by Baral et al. was chosen to serve as the foundation of this PhD research in conjunction with the principles of Implementation Science. The model was used to situate and guide holistic thinking in designing each stage of the research, developing the research questions and objectives, designing the TAPS study, and developing analyses of the data. In this regard, the holistic nature of considering multiple social and environmental facets was critical in being able to understand how and why women would engage with the PrEP intervention, in terms of applicability and acceptability. It also helps to highlight where there might be gaps in knowledge in relation to intervention development. The model fits within the principles of Implementation Science to organise data into relevant categories starting from, or ending with, the individual. These categories span across the domains of practical delivery and user perspectives which have been the basis of this research.

It is important to note, that the social ecological model is not a theory for change or decision making, but rather a framework for conceptualizing environments (113), and was used in this way throughout this research. A slight adaptation of the MSEM was developed for the FSW context in South Africa as shown in Figure 6. The adaptations include defining the individual at risk as a FSW, and then incorporate additional specificity in the other spheres in terms of how they relate to FSWs and their specific risk contexts. One other additional element is HIV prevention which is illustrated as spanning across all of the spheres.

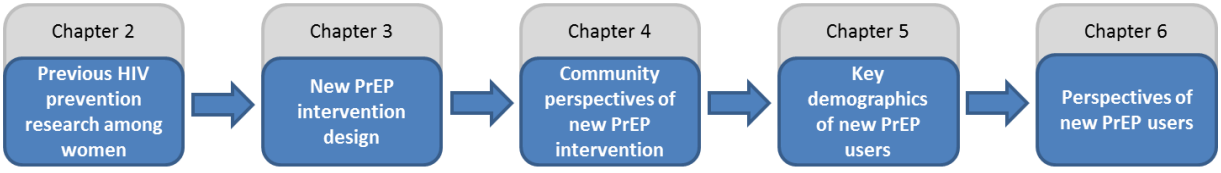
Figure 6. PhD Modified Social Ecological Model for FSWs in South Africa



1.11.4. Thesis narrative and structure

This thesis is presented in research or journal paper style consisting of six research papers included as methods and results in chapters with chapter specific introductions at the beginning of each. Each chapter addresses key research questions arising from the PhD objectives. The research follows a flow of inquiry and learning as shown in Figure 7.

Figure 7. PhD research flow



Chapter 2 addresses the question: *What are the motivations and barriers to uptake and use of female-initiated HIV prevention products in sub-Saharan Africa?* This was a key question to address in order to explore the vast literature concerning HIV prevention for women, and to

establish their perspectives on use. PrEP is the latest in a long line of product research, and much can be learned for successful implementation by carefully examining reactions and responses to the products and research that came before. There are two papers in this chapter aimed at answering this question. Paper 1 is a methods paper in the form of a protocol for the systematic review conducted as part of this body of work. The protocol presents a novel methodological approach to an adapted-meta ethnography exploring the motivations and barriers to uptake and use of female-initiated, primary biomedical HIV prevention technologies in sub-Saharan Africa. This protocol was published in the BMC journal Systematic Reviews in 2015 (114). Paper 2, is the adapted meta-ethnography itself presenting results of the search and synthesis of the data which was submitted to BMC Public Health in 2016 and has been provisionally accepted pending revisions.

Chapter 3 focuses on the question: *What are the practical and contextual factors which might affect the uptake and use of PrEP among FSWs in South Africa?* Also a methods paper, Paper 3 describes the formative research process and lessons learned through an iterative, grounded approach used in developing the PrEP and early ART interventions developed for the TAPS Demonstration Project. The details reported in this paper represent the first lessons learned regarding how and why PrEP might be taken up among FSWs in South Africa, and describes how the intervention was developed for implementation and evaluation. This paper was submitted to BMJ Open in July 2017 and is currently awaiting editorial decision following peer review.

Chapter 4 addresses the question: *What are the community-level perceptions of PrEP in terms of acceptability within the context of imminent implementation among FSWs in South Africa?* Paper 4, an in-depth look at the FSW community perspectives of impending PrEP implementation, captures women's perceptions of PrEP immediately before the launch of TAPS when PrEP will first be offered in this population. The FGD results presented in this paper build on the learning from the systematic review and represent the final piece of the formative research. This paper was submitted to the Journal of the International AIDS Society (JIAS) in July 2017.

Chapter 5 addresses the question: *What are key characteristics of FSWs who take up and use PrEP?* In addition to wanting to understand women's uptake and use of PrEP in the demonstration project, it was also important to understand the characteristics of women taking it up in this early stage of implementation. Paper 5, which is the primary analysis paper

for the TAPS project, includes the key demographic and behavioural characteristic results of the PrEP users in TAPS. This paper was submitted to a special edition on PrEP at PLoS Medicine in July 2017. Revisions following reviewer comments are under final review with the journal.

Chapter 6 is the final results chapter and addresses the question: *What are the perspectives and lived experiences of FSWs taking up and using PrEP in South Africa?* Paper 6, presents an in-depth view of individual PrEP user perspectives through an analysis of serial in-depth interviews. These are new PrEP users accessing the product and intervention in a 'real world' clinic for the first time, and the analysis of their perspectives builds on the previous work leading up to this point. This paper will be submitted to Social Science and Medicine.

The thesis concludes with a discussion section including a summary of the key themes and findings, strengths and limitations, as well as recommendations for policy and practice, and future research. Note that references will be included separately in each section accordingly, and that each paper is preceded by an LSHTM Cover Sheet for research papers included in a research thesis. Where additional description of methods used or background information is needed beyond what can be included in a research manuscript for publication, this is included in the chapter introductions.

1.12 PhD Funding and Support

This research was conducted as part of a staff PhD at the London School of Hygiene and Tropical Medicine, and supported by several grants. The first grant supported the systematic review research and was from the Bill and Melinda Gates Foundation as part of a consortium on PrEP organised through Georgetown University. The formative research for TAPS, including the FGDs, was mostly funded through a grant from AIDS Fonds Netherlands. The main TAPS research, which included the quantitative demographic and behaviour data, as well as the IDI data, was funded through a grant awarded to Wits Reproductive Health and HIV Institute from the Bill and Melinda Gates Foundation (grant number: OPP1084416). Additional monetary support for the TAPS project came from the United States Agency for International Development (AID-674-A-12-00034). Study drugs for PrEP in TAPS were donated by Gilead Sciences.

1.13 PhD Ethics Considerations and Approvals

All of the research presented here has been approved by the London School of Hygiene and Tropical Medicine Ethics Committee (reference numbers: 5622 and 10102). The focus group

discussions for TAPS were approved separately by the Wits Human Research Ethics Committee (HREC) (reference number: 140502; Appendix ii). The main TAPS research, including all data presented here, was also approved by the Wits HREC and the South African Medicines Control Council as shown in Appendices iv and v (reference number: 20140740). All participants signed separate informed consent forms for the FGDs, main TAPS research, and separately for the IDIs. These forms are attached in Appendices vii, ix, and xi.

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2.0 Chapter 2: What do women want? A qualitative meta-exploration of women's perspective of female-initiated HIV prevention methods in sub-Saharan Africa.

2.1 Introduction

This chapter addresses the research question associated with Objective 1 of this PhD: *What are the motivations and barriers to uptake and use of female-initiated HIV prevention products in sub-Saharan Africa?* Before embarking on designing new research on uptake and use of PrEP among FSWs, it was important to investigate the existing literature on women's preferences for and values in relation to HIV prevention methods or products, in particular the ones over which they could initiate and maintain control. It was a conscious choice not to limit this review to FSWs only, as first and foremost they are women and share the foundational issues of women in general. This was an important exercise in order to establish a base of knowledge around what women wanted out of HIV prevention beyond physical attributes, and delve into what would influence or deter uptake and use within women's lives.

This chapter includes a methods paper in the form of a protocol published in BMJ Open in 2015. The protocol paper has been included since it describes in detail the process undertaken to conduct the systematic review, which included a novel methodological approach combining an adapted meta-ethnography of data synthesis and a weight of evidence review which comparatively assessed the papers included in the review. The development of these methods was supported by a library specialist and an expert in evaluation of literature. Prior to conducting the review, an informal, systematic review of reviews was conducted to establish whether any review was previously published. This originally looked for reviews on determinants of uptake and use of HIV prevention interventions among women in sub-Saharan Africa, but was expanded to search for qualitative reviews as well. The databases searched were Health-evidence.ca, Cochrane, Medline, Systematic Review Journal, Database of Abstracts of Reviews of Effects (DARE), and International Prospective Register of Systematic Reviews (PROSPERO). The search strategy used in this effort were adapted from validated search strategies by combining concepts from published systematic review searches and disease specific searches (1,2). Out of a total of 1515 hits from the six different databases, there were no papers that matched the topic. Concepts for building a search strategy for the eventual meta-ethnography were collected through this review and further developed through

reviewing key qualitative literature and the handful of other meta-ethnographies previously conducted, which are referenced in more detail in the papers included in this chapter.

The results of these methods are presented in the meta-ethnography paper in this chapter which explores women's perceptions of use of a limited array of HIV prevention products. These results provided the basis of thinking for developing the research tools and direction of inquiry employed throughout the rest of the PhD. This results paper was accepted for publication, pending final review of revisions, in BMC Public Health in September 2017, following a year-long process of review.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Social Science and Medicine
Please list the paper's authors in the intended authorship order:	Robyn Eakle, Rutendo Bothma, Adam Bourne, Sanele Gumede, Keneilwe Motsosi, Helen Rees
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the research tools with support from Dr. Bourne. I oversaw data collection and led the analysis. I drafted the manuscript.

Student Signature: [redacted] **Date:** 5 October 2017

Supervisor Signature: [redacted] **Date:** 5 October 2017

2.3 Protocol for a systematic review: understanding the motivations and barriers to uptake and use of female-initiated, primary biomedical HIV prevention technologies in sub-Saharan Africa.

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2.3.1 Abstract

Background

Women in sub-Saharan Africa are disproportionately affected by high rates of HIV, yet relatively few products exist for female-initiated HIV prevention. New ARV-based prevention options could present opportunities for women to expand their HIV prevention choices, however acceptability and adherence plays a key role in the effectiveness of these products and implementation is still in early stages. To better understand which HIV prevention options might best serve women in sub-Saharan Africa, how and why, this review will explore qualitative evidence from clinical trials and implementation studies alike using a meta-ethnographic approach to synthesize data and interpret results.

Methods

This systematic review will use a meta-ethnographic approach to analyse qualitative data extracted from multiple studies featuring actual use of female-initiated technologies for HIV prevention. The search strategy will be applied in seven databases and papers will be selected using strict inclusion and exclusion criteria. The review will closely follow the guidance set forth by PRISMA and CRD where the guidance applies to qualitative data. Two reviewers will review all papers during the paper selection phase, with consultation from a third reviewer to confirm consensus. All papers included in the review will be read and analysed by two reviewers. The final analysis will be conducted by three primary reviewers with additional input from all other authors.

Discussion

With new HIV prevention technologies currently in early implementation phases and still more on the horizon, there is much to learn about how best these products may be delivered. A review such as this could help to inform the real-world implementation of the next wave of new HIV prevention technologies such as ARV-based oral pre-exposure prophylaxis (PrEP).

2.3.2 Background

New HIV infections in sub-Saharan Africa persist at high rates where women, in particular, are disproportionately affected (4). In South Africa, a survey published by the Human Sciences Research Council in 2012 estimated the national prevalence rates among women between the ages of 20 and 49, to be between 17.4% to 31.6% (5). Current methods for HIV prevention have taken the field only so far, but to further reduce new infections, new options for prevention are needed.

There are several approaches men and women can take to prevent the acquisition or transmission of HIV. Currently, these include: the use of male or female condoms; medical male circumcision; or the use of post-exposure prophylaxis (PEP), an anti-retroviral (ARV) drug based regimen given after suspected exposure to HIV. The majority of these prevention options, aside from PEP, are either entirely or partially controlled by men, or their use is dependent upon male acceptance. Male condoms require mutual agreement for use, and while the female condom can be initiated by women, it difficult for them to do so covertly. Additionally, research has suggested that female condoms are often difficult to access, and not always acceptable or easy to use (6). PEP has typically only been available or accessible for specific circumstances, such as post-rape care (7), and the limited implementation suggests there may be significant intervention capacity issues relating to the training and education of healthcare providers (7,8). The diaphragm has been tested as an option for preventing HIV infection, and shown to have no effect (9), although efforts have been renewed to revive it as an option by redesigning the product and adding a microbicide. Studies published in the last 5 years (10,11) indicate that ARV-based HIV treatment has also been shown to have a powerful secondary prevention effect by the suppression of an infected individual's viral load, however, the population-level impact of this will take time and is unlikely to control the epidemic on its own (12).

A new primary prevention option utilising ARV-based medication has shown significant promise. Development of a variety of products (including pills, intravaginal microbicide gels, films and intravaginal rings) has yielded a new first-generation option in the form of a daily pill-based regimen, called pre-exposure prophylaxis (PrEP). Six recent clinical trials testing oral PrEP have shown varying levels of overall efficacy (13–16), from 44% to 75%. At present, however, the indication is currently only registered in the United States. The varying degrees of efficacy from the oral PrEP trials can mostly be attributed to adherence, or consistent and correct use of the products (17). The FEMPrEP trial, consisting only of women, was stopped for

futility, while the VOICE trial was partially stopped for futility, with the final arm continuing to a flat result (18,19). These findings have caused researchers and implementers alike to question whether adherence dependent ARV-based prevention options would actually be effectively taken up by women and make a significant contribution to HIV prevention. Analyses of qualitative and mixed method research from these trials are underway, along with additional follow-up studies to better understand why women did not use the products. Two papers already published on this area have revealed important insights as to the reasons women did not use the products, including: misaligned incentives for participating in the trials (money and access to better services); ambivalence about the research resulting in non-use of the products; a lack of understanding of the need to accurately report actual product use; and misperceptions of personal risk of HIV (20,21). This has shown that non-use of the products often had little to do with the products themselves and more to do with contextual issues, which may mean that oral PrEP could still be a viable prevention option if offered to suitably motivated users. This perspective is reinforced by recent results from the FACTS001 trial, which evaluated the efficacy of tenofovir-based intravaginal microbicide gel and established the gel not to be efficacious in preventing HIV acquisition, largely as a result of complex behavioural/social factors, as well as possible biological ones (22).

Given the complexities highlighted in the PrEP efficacy trials about delivering and implementing new prevention options, it is important to understand women's perspectives and what factors determine the use of emerging biomedical technologies. This is essential not only to understand how existing HIV prevention options may be better implemented, but also to inform the delivery of the next wave of technologies, such as oral PrEP, as well as other new products further upstream in the development pipeline, such as vaginal rings containing microbicides and injectables. To date, a number of studies have explored the acceptability of HIV prevention technologies, including those already licensed for widespread use and those in development or clinical trial phases, as well as other contextual factors that function as motivators or barriers to their use. Studies producing qualitative data, like those stemming from the failed oral PrEP trials, are imperative for understanding what people think, as well as how and why they make decisions regarding uptake of HIV prevention options.

This systematic literature review will explore, synthesize, interpret and present the key factors that motivate or deter uptake and use of prevention technologies for women in sub-Saharan Africa. Such a review can help to inform the development and roll-out of new technologies as they become available. This review will focus on female-initiated technologies, which are those

women administer themselves, and can be technologies already available in the market or in the development phase. Data included in the review will be drawn from studies of actual product use, rather than hypothetical investigations. Technologies included in the review will include: PEP, PrEP, vaginal microbicides, the diaphragm and the female condom. While the diaphragm is not currently an accepted, efficacious method for preventing HIV, the research conducted around experiences with use will be included in this review as these may provide transferable insights into other product use. Qualitative research is best suited to the exploration of personal experience and decision making. Given its focus on the motivations and barriers to the uptake and use of technologies, the review will focus on the synthesis and analysis of qualitative data only, utilising a meta-ethnographic approach.

2.3.3 Methods and Design

This is a systematic review using a meta-ethnographic approach to analysis. As such, the review will include only qualitative data extracted from studies identified through intensive, systematic searches, and will closely follow the guidance set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the Centre for Reviews and Dissemination (CRD). This review has not been registered on PROSPERO as since it is a review of qualitative evidence it does not qualify. As a result, there is no PROSPERO number associated with this review.

The primary objective of this review is to identify and understand the motivations and barriers affecting uptake and use of female-initiated, primary biomedical HIV prevention technologies for women in sub-Saharan Africa. The review will incorporate the following secondary objectives:

- To identify types of studies from which data are extracted (e.g. stand-alone qualitative/social science, implementation or service delivery evaluation, or clinical trials);
- To describe elements of uptake and use of specified technologies by sub-population (e.g. female sex workers, victims of rape, or young women);
- To describe factors that influence uptake and use by intervention;
- And to identify priorities for future research.

Search Strategy

The search strategy incorporates four primary concepts: HIV; uptake and use; qualitative research; and sub-Saharan Africa. Search strategy concepts have been constructed using an iterative process. Search terms will be adapted across databases to account for variations in subject headings. The following databases will be included in the search: Africa-wide Info, CINAHL, Embase, Global Health, Medline, Psychinfo, and Web of Science. The Medline search strategy was developed as the primary search strategy template and will be adapted for the other databases.

Inclusion and Exclusion criteria

Papers will be selected during the screening process using the following inclusion criteria:

- Population: Adult women, age 18 and above
- Intervention: Female-controlled, biomedical – PrEP/microbicides, PEP, female condom, and diaphragms
- Comparator: Not relevant
- Outcome: Narrative on the motivations or barriers to HIV prevention uptake and use
- Study Design: Qualitative studies – interviews or focus groups
- Study type: Studies must be based on primary research where products have been made available for actual use
- Location: sub-Saharan Africa

Exclusion criteria are as follows:

- Any papers published on research occurring before 2003
- Reviews
- Any studies based on hypothetical or potential use of products not made immediately available at the time of the research
- Any data not from the women's point of view as the user
- Any research from the perspective of HIV-positive women
- Any research based on secondary prevention technologies or interventions (e.g. PMTCT)

Papers will be excluded from the review if they do not meet all of the criteria above. Papers will not be excluded according to a quality assessment, per se, but will be evaluated according to principles and practices as outlined below. There will be no limitation by language, and grey literature will be included if identified through the database searches or through consultation with relevant experts.

The concept of experience of actual use is central to this review. As such, we will include data from studies conducted in both trial and implementation settings. It may be argued that incentives could be quite different in a trial setting where participants are paid to come to a clinic as compared to a 'real-world' setting where patients come when they feel they need to. From this perspective, trial participants could be more incentivised to attend the clinic. However, in the case where new prevention options proven to protect against HIV are available, the accessibility of the product or intervention may be the incentive to come to the clinic. Clearly, there are a variety of motivators for engaging in health related behaviour, which we hope to explore in the context of female-initiated HIV prevention. In this review we hypothesize that some of the experiences of actually *using* the products should be similar regardless of initial motivation. Additionally, some HIV prevention trials were stopped early or ended with a flat result because of non-use. In this paper, we aim to elucidate the issues leading to non-use across both the trial and the clinic settings, and hypothesize that reasons for non-use are likely to be similar. We will also compare between the two setting types to highlight any differences.

The year 2003 was chosen as the cut off point for selecting papers as it marks the establishment of PEPFAR and the wide-scale introduction of antiretroviral therapy (ART) for HIV treatment in Africa. With the introduction of effective medication regimens, general population views of HIV and the means by which its transmission could be managed began to change (23).The rollout of ART in Africa significantly changed the approach to the epidemic in sub-Saharan Africa which, until this time, largely consisted of efforts to promote condom use and HIV testing with the aim of preventing new infections; this had limited success as people testing HIV-positive could not access life-saving medication. Although treatment was not uniformly rolled out simultaneously in all countries in 2003, the launch of PEPFAR and increased access to ART renewed hope and motivation to prevention efforts and is attributed to the turn of the epidemic in Africa (24).

Screening Process

All references will be uploaded into a reference manager database and duplicates removed before starting the paper selection process. After de-duplication, all papers will be reviewed by title and abstract according to the inclusion and exclusion criteria by two reviewers. Any discrepancies between reviewers will be discussed and mediated by a third researcher. Once papers have been selected by title and abstract, three reviewers will review papers by full-text according to the inclusion criteria. Decisions regarding inclusion of papers from the same study will occur through discussion with all three reviewers on a case by case basis. All papers selected by the reviewers will be discussed by all three reviewers to reach consensus and confirm inclusion.

Data Extraction, Analysis and Synthesis

This review will be conducted as a meta-ethnography. This process of analysis will follow the principles set out in Noblit and Hare (25), but will use a form of this method as adapted more recently by several researchers (26–28). Specifically, this adapted form of meta-ethnographic synthesis allows for qualitative data collected through methods beyond ethnography**, such as** interviews and focus groups, to be combined and interpreted to derive meaning and understanding of data across different types of studies.

Once papers for inclusion have been finalized after full-text review, reviewers will be assigned papers for data extraction according to the data extraction tool developed for the review. A thematic framework will also be constructed through the data extraction phase in an iterative fashion, with input from all reviewers. A minimum of two reviewers will extract data from each paper; consensus will be reached with input from the third reviewer on any differences in extracted data. The thematic framework will be used to build the meta-ethnographic constructs which comprise three layers: the perspective of the participants, the perspective of the authors, and the perspectives of the researchers conducting this review. These layers are often fluid and may overlap where the perspectives of the authors cannot always be divided from those of the participants, but eventually, these two initial layers lead into the construction of the final layer in which new understanding can be developed by looking across all of the data at once.

Quality Assessment

In contrast to quantitative research, there has been considerable debate over how to assess the quality of qualitative research (29–32). Inherent to qualitative research is a flexible,

iterative, and pluralistic process which is guided by the context in which it is conducted and by the research subjects themselves. Several authors have argued that it is not typically an undertaking easily standardized by checklists, which could actually hinder the creative nature of the work. Instead, there are accepted practices, or fundamental principles, by which one can analyse the research (30,33). An approach often adopted is the 'The weight of evidence review', which first establishes elements of good research and those elements are then taken into account when looking across all of the papers included in a review (34). This enables an assessment of the quality of the literature so that the review can be judged as a whole, rather than evaluating individual elements of each paper. In this review, a combination of the fundamental principles and weight of evidence review may be employed to judge the overall level of quality of papers included.

Anticipating Limitations and Bias

As with any research study, the authors recognise that there will be limitations to this particular review.

Some components of the qualitative research included in individual studies may have been excluded from publication due to limits enforced by the publisher. Often, in-depth descriptions of methods, and development of the research and process through which it was undertaken, are left out of the publications, making it difficult to assess quality of the research process and the awareness of the researchers' positions within their own research (reflexivity). Inevitably, these exclusions would affect the potential scope of qualitative evidence available for this review.

It is possible that some research may be absent altogether from the searchable and published literature. Research has shown that around 44% of conference abstracts on qualitative research are translated into papers published in journals - which is about the same rate as for quantitative research (35). Additionally, while this review will not exclude grey literature, the constraints of web-based searching and the lack of systematic, online grey literature indexing means it is difficult to determine whether our search has successfully captured all relevant grey literature.

2.3.4 Discussion

This systematic review, using a meta-ethnographic approach for analysis, is the first of its kind to synthesize qualitative data across a wide and complex body of literature in this subject area. The ultimate aim of this study is to learn from research already conducted on women's experiences of HIV prevention technologies and their motivations to take up and use them (and barriers to doing so), in order to inform the real-world implementation of the next wave of new technologies such as oral PrEP. Ultimately, these findings can help with future programming design, decisions, and research to optimize delivery of existing and new HIV prevention interventions for women across sub-Saharan Africa.

Authors' Contributions

RE conducted pre-research, designed the review, developed search strategy, and drafted manuscript; CJ provided input on design, developed search strategy, and edited manuscript; AB provided input on search strategy and design, and edited manuscript; JS provided input on design and edited manuscript; HL provided input on design and edited manuscript. All authors reviewed and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Social Science and Medicine
Please list the paper's authors in the intended authorship order:	Robyn Eakle, Rutendo Bothma, Adam Bourne, Sanele Gumede, Keneilwe Motsosi, Helen Rees
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the research tools with support from Dr. Bourne. I oversaw data collection and led the analysis. I drafted the manuscript.

Student Signature: [redacted] **Date:** 5 October 2017

Supervisor Signature: [redacted] **Date:** 5 October 2017

2.4 Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography

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Number of figures/tables: 3/1
References: 56

Key words: HIV prevention, biomedical prevention products, pre-exposure prophylaxis (PrEP), women, qualitative research

2.4.1 Abstract

Background

Women bear a disproportionate burden of HIV throughout the world prompting extensive research into HIV prevention products for women which has met with varied success. With an aim of informing future policy and programming, this review examines the barriers and motivations to the uptake and use of female initiated products in sub-Saharan countries.

Methods

We conducted a systematic review as an adapted meta-ethnography of qualitative data focused on actual use of products. After deduplication, 10,581 and 3,861 papers in the first and second round respectively were screened. Following the PRISMA guidance, 22 papers were selected and synthesized using Malpass's definitions of first, second, and third order constructs. First order constructs, consisting of participant data published in the selected papers, were extracted and categorised by second and third order constructs for analysis. A weight of evidence review was conducted to compare and assess quality across the papers.

Results

The 22 papers selected span 11 studies in 13 countries. We derived 23 second order constructs that were translated into seven overarching third order constructs: Sexual Satisfaction, Trust, Empowerment and Control, Personal Well-being, Product use in the social-cultural environment, Practical Considerations, Risk Reduction, and Perceptions of Efficacy. Relationships and trust were seen to be as or more important for product use as efficacy. These constructs reveal an inherent inter-relationality where decision making around HIV prevention uptake and use cannot be binary or mono-faceted, but rather conducted on multiple levels. We developed a framework illustrating the central and proximal natures of constructs as they relate to the decision-making process surrounding the use of prevention products.

Conclusions

Health systems, structural, and individual level HIV prevention interventions for women should adopt a holistic approach. Interventions should attend to the ways in which HIV prevention products can serve to reduce the likelihood of HIV transmission, as well as help to protect partnerships, enhance sexual pleasure, and take into account woman's roles in the social environment. Stigma, as well as sexuality, is likely to continue to influence product uptake and use and should be prominently taken into account in large-scale interventions.

2.4.2 Introduction

Women bear a disproportionate burden of HIV infection across the world, and in particular in sub-Saharan Africa (1). Until recently, the only readily available HIV prevention options for women have been male condoms. Female condoms were at one time a promising new option, however lack of support from international agencies and funders translated into challenges in delivery and access (2–4). This meant that male condoms have remained the dominant form of HIV prevention for decades. Additionally, post-exposure prophylaxis (PEP), while proven to be efficacious in preventing HIV acquisition (5,6), has generally only been available for health workers and rape victims (7,8).

Advances in HIV prevention research have yielded a new approach: pre-exposure prophylaxis (PrEP). PrEP is the use of antiretroviral drugs taken orally by people who do not have HIV to prevent acquisition of the virus. A recent systematic review of oral PrEP including 18 studies found that " PrEP use with greater than 70% adherence demonstrated the highest PrEP effectiveness (RR=0.30, 95% CI: 0.21-0.45, p<0.001) compared to placebo", confirming that oral PrEP will prevent HIV with high rates of efficacy when taken consistently (9). This review did not include one study completed with people who inject drugs (10), which found a moderate but significant level of efficacy, nor did it include two microbicide gel[3] studies (CAPRISA004 and FACTS001), the results of which together did not prove product efficacy (11,12). The non-significant levels of efficacy in the two microbicide trials, as well as the similar results of the VOICE (comparing oral PrEP and microbicide gel) and FEMPrEP (oral PrEP only) trials were either partially or largely due to poor adherence (13,14), opening up questions around the ability to take oral PrEP effectively.

Qualitative research conducted as part of these clinical trials has explored reasons for poor adherence. Reasons range from apathy towards the research itself, dislike of product side effects, lack of privacy in which to use the products, low risk perception, and access to better healthcare offered in studies as primary motivation for study participation (15,16). The insights arising from these studies, conducted primarily in sub-Saharan Africa and India, combined with lessons learned from past research of other HIV prevention products will provide the field with further understanding of why and how women take up and use HIV prevention products, which can inform better implementation.

3 Microbicide gel can also be referred to in the literature as topical PrEP, however, in this review we have kept is as microbicide gel, or just gel.

This is a systematic literature review conducted in the form of a meta-ethnography to synthesize qualitative findings from research on the practical use of HIV prevention products among populations of women across sub-Saharan Africa. Broadly, our aim is to inform future policy and programming for HIV prevention products for women going forward, by drawing on the wealth of information already published from the research conducted in sub-Saharan Africa. As such, the primary objective of this review is to identify and understand the motivations and barriers affecting uptake and use of female-initiated, primary biomedical HIV prevention products for women in sub-Saharan Africa.

2.4.3 Methods

We conducted a systematic review using a meta-ethnographic approach following the principles set out by Noblit and Hare (17). This approach allows for a sophisticated and robust manner of synthesis as compared to a typical literature review of qualitative data, and focuses on interpretation through analysis of constructs rather than summarization of themes (18). For this review, we conducted an adapted meta-ethnography as defined more recently by several researchers (19–21), which allows for qualitative data collected through a variety of methods, such as interviews and focus groups, as well as ethnographies, to be combined and interpreted. Qualitative data are best placed to answer the questions around how and why products are utilised effectively, rather than measuring only their uptake or adherence. Throughout this process, we also employed the guidance set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the Centre for Reviews and Dissemination (CRD) (22,23). The protocol for this review has been published and the methods described in more detail (24).

This review was not registered on PROSPERO since reviews of qualitative evidence are not currently included on the PROSPERO database. Additionally, the original protocol articulated “female-initiated HIV prevention technologies” in the title, however we chose to change technologies to products in the final paper.

Search Strategy and Inclusion Criteria

We searched seven databases: Africa-wide Info, CINAHL, Embase, Global Health, Medline, Psychinfo, and Web of Science. The search strategy comprised four primary concepts: HIV prevention; uptake and use; qualitative research; and sub-Saharan Africa, which were first confirmed through iterative pilot searching in Medline, and then adapted for the other

databases. The first set of searches was conducted in July of 2013, and then again in July of 2015.

Papers were included in the review if they met the following criteria: women aged 18 and above; data focused on female-initiated products (oral PrEP, microbicide gel, PEP, female condom, vaginal ring, and diaphragms); included narrative on motivations and/or barriers to uptake and use of products; qualitative research; located in sub-Saharan Africa; and, research conducted from 2003 or later. Note that female-initiated product refers to any HIV prevention product that can be initiated and used exclusively by women without requiring the involvement or permission of a partner.

Actual experience of product use was central to this review, rather than hypothetical acceptability studies (e.g. where study participants did not actually have access to products). Since few studies have been published in 'real-world' programme settings, we also included data from across research settings, both randomized control trial and implementation. While incentives to participate in research could be quite different to clinic attendance, in this review we hypothesized that experiences of actual product use should be similar regardless of initial motivation. Additionally, we have included women's perspectives on use of the diaphragm and vaginal microbicide gels, despite the limited efficacy of these products to prevent HIV. At the time of those studies, efficacy was unknown, and importantly, women's experiences and perceptions of use extend beyond efficacy. The interest of this review is to examine the elements that would make a product feasible and relevant for a woman to use it, and what those salient elements are across products.

We did not limit our search by language, and we allowed for grey literature to be included, however none was identified through our searches or through consultation with relevant subject matter experts. Studies were excluded if they focused only on hypothetical use of products or represented perspectives from the male point of view, HIV-positive women only, or secondary prevention products (e.g. Prevention of Mother to Child Transmission).

Screening and Selection Process

All 25,861 references identified through searching were uploaded into the reference software manager Mendeley. After de-duplication, two reviewers screened all 10,580 papers by title and abstract according to the inclusion and exclusion criteria. Any discrepancies between reviewers were discussed and mediated by a third researcher. The papers were identified first

by title and then by abstract, and were then reviewed in duplicate by three reviewers. There were several cases of papers published from the same study, however we determined no overlap of data therefore these papers were all included. The 39 papers identified for possibility for inclusion were discussed by the three primary reviewers during which some were eliminated mainly due to inability to isolate female-centred data from male, or due to the research being conducted before 2003. Finally, 22 papers were selected for analysis. This process is illustrated in Figure 1.

Analysis and Synthesis

Data were extracted from the papers by two reviewers, then sorted by themes and incorporated into a construct worksheet. To generate the concepts for our constructs, we employed Malpass's definition of the first, second, and third order constructs (25) used previously by authors of other similar reviews (19,20). First order constructs consist of participant data published in the selected papers, and were extracted and categorised by second and third order constructs for analysis. Second order constructs consist of author perspectives of their manuscript data extracted from the papers, and third order constructs are thematic categories developed through our analysis. In this regard, our construct worksheet comprised three meta-ethnographic layers: the perspective of the participants, the perspective of the paper authors, and the perspectives of the researchers conducting this review. We then used the process of concept translation, as described by Musheke et al (20), to arrive at our synthesized third order constructs.

Weight of Evidence Review

We employed a weight of evidence (WoE) review to assess the relative strength of the papers included in the review. A WoE review, as defined by Gough et al (26), is a process by which standard elements of research are identified in each paper included in the review, and then assessed in comparison with one another to judge the overall strength or quality of the papers (26). The results of our WoE are listed in Table 1. This process uses a systematic approach similar to the GRADE process used by the World Health Organization (WHO) in assessing the quality of quantitative studies included in systematic reviews in support of guidelines. Each paper was assessed in terms of relevance (how directly the paper answered the aim of the review), appropriateness of study design, and soundness (which equates to the inclusion criteria for this review).

Figure 1. PRISMA chart of review process

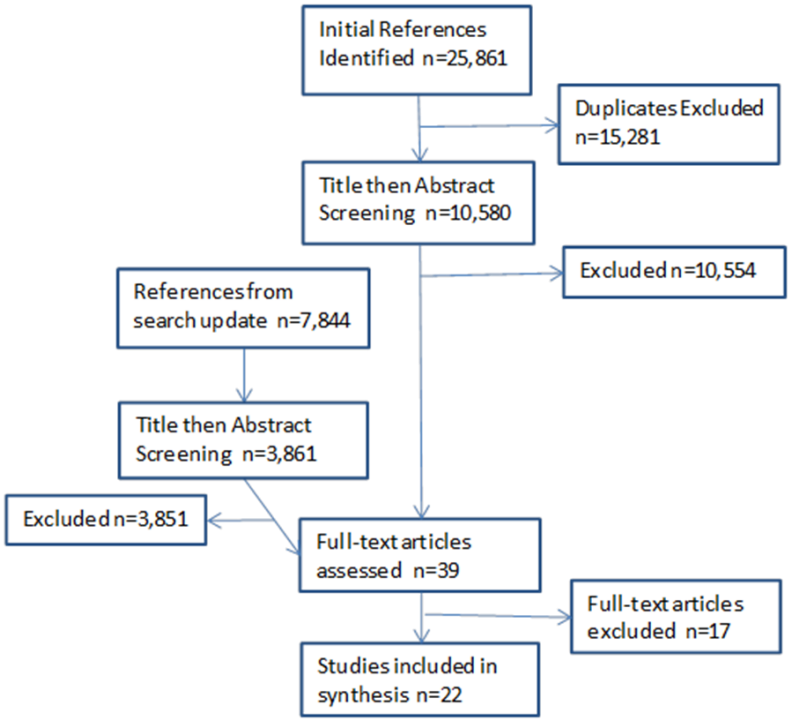
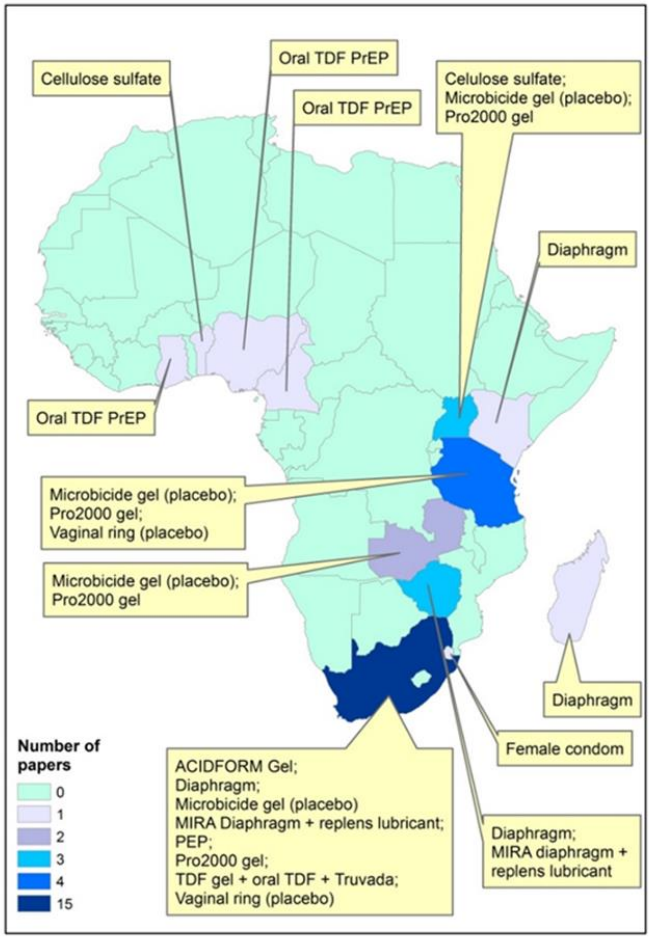


Figure 2. Map indicating HIV prevention products for women and sub-Saharan countries featured in the review papers



2.4.4 Results

The 22 papers included in the review represent 11 studies (including ancillary research as part of larger studies) across 13 countries in sub-Saharan Africa, as shown in Figure 2. Since the review covers studies conducted between 2003 and 2015, more papers describe experiences using products such as diaphragms and microbicide gels, as compared to more recent products such as oral PrEP for which few papers have yet been published.

We derived 23 second order constructs that we translated into seven overarching third order constructs, mapped in Table 2. The results presented here are organised by third order construct labels. The findings are organised in this way to best illustrate and organise the fluid and inter-relational nature of the themes, which are illustrated in Figure 3. This is instead of a more binary presentation which has been characteristic of other such reviews (19,20). It is also important to note that while this review offers a synthesis of the findings and an overview of the primary themes present in this diverse literature, it was not possible to capture every nuance in all of the selected papers.

Weight of Evidence Review

The WoE review found a relatively high level of quality across the body of evidence included in this adapted meta-ethnography. No one category scored lower than medium. Rather we found many medium-high and high ratings. Some papers came from ancillary or imbedded trial research which may not be considered 'real-world', and many did not explicitly focus on answering the overall aim articulated in this review. However, these papers were still included because they contained data directly responding to the review aim. All of the studies were conducted with strong, clear methodologies which led us to give the evidence overall a high rating.

Table 1. List of papers and Weight of Evidence Review

Authors	Title	Pub Year	Product	Data Type	Study Context	Location	Pop	N	Study Dates	Theory	Soundness	Appropriateness of study design	Relevance	Overall Rating
Abrahams; et al	Barriers to post exposure prophylaxis [PEP] completion after rape: a South African qualitative study	2010	PEP	IDIs	Stand-alone qualitative	South Africa	Victims of sexual assault	29	2005-2006	Not specified	Medium-High: no theoretical approach articulated for study	High: standalone qualitative research	High: though an outlier, specifically discusses barriers to PEP use	High
Behets, Frieda M T F; et al	Evidence-based planning of a randomized controlled trial on diaphragm use for prevention of sexually transmitted infections	2008	Diaphragm	FGDs	Formative, qualitative	Madagascar	Female sex workers	266	2004	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a formative research activity, mixed methods	Medium-High: qualitative research focusing on acceptability, data on motivations and barriers come through	Medium-High
Gafos, Mitzy; et al	Intravaginal insertion in KwaZulu-Natal: sexual practices and preferences in the context of microbicide gel use	2010	Pro2000 gel	IDIs and FGDs	MDP 301 Phase III RCT	South Africa	Sexually active adult women/trial participants	136	March 2006 - August 2008	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium-High: qualitative research on vaginal practices	Medium-High
Greene, Elizabeth; et al	Acceptability and adherence of a candidate microbicide gel among high-risk women in Africa and India	2010	Celulose Sulfate	IDIs	Phase III RCT	Uganda, Benin	High risk women/trial participants	30	Feb-Aug 2007	A variation of the socio-ecological model (Mcleroy et al. 1988)	High - all details included	Medium-High: qualitative research within a larger trial setting	High - specifically evaluates barriers to use of gel among users	High

Guest, Greg; et al	Changes in sexual behaviour during a safety and feasibility trial of a microbicide/diaphragm combination: an integrated qualitative and quantitative analysis	2008	ACIDFORM Gel and Diaphragm	IDIs and FGDs	Safety and Feasibility study	South Africa	Sexually active adult women	120	April 2004 - Nov 2005	Data analysis conducted within a positivist framework (Bernard & Ryan, 1998), no specific theory for study	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium: paper is focused on changes in sexual behaviour and not motivators/barriers to use, although these come out in the data	Medium-High
Guest, G; et al	Acceptability of PrEP for HIV prevention among women at high risk for HIV	2010	Oral TDF PrEP	IDIs	Phase III RCT	Nigeria, Cameroon, Ghana	Sexually active adult women/trial participants	24	June 2004-March 2006	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium-High: qualitative research focusing on acceptability, data on motivations and barriers come through	Medium-High
Kacanek, Deborah; et al	A qualitative study of obstacles to diaphragm and condom use in an HIV prevention trial in sub-Saharan Africa	2012	Diaphragm	FGDs	MIRA Trial phase III RCT	South Africa and Zimbabwe	Sexually active adult women/trial participants	206	Aug 2006 - Jan 2007	Modified grounded theory (Glaser & Strauss, 1967) for analysis, no specific theory for study	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium-High: data focused on ability to use condoms with diaphragm, though barriers to use of diaphragm came through	Medium-High
Mathenjwa, T & Maharaj, P	Female condoms give women greater control': A qualitative assessment of the experiences of commercial sex workers in Swaziland	2012	Female condom	IDIs and FGDs	Stand-alone qualitative	Swaziland	Female sex workers	25	Jan - May 2010	Not specified	Medium-High: no theoretical approach articulated for study	High: standalone qualitative research	High: specifically looks at experiences, motivations and barriers to use of female condom	High

Montgomery, C M; et al	The role of partnership dynamics in determining the acceptability of condoms and microbicides	2008	Pro2000 gel	IDIs	Component of pilot study for MDP 301 phase III randomized trial	South Africa, Tanzania, Uganda and Zambia	general population women in couples	45	Not specified	none specified (though used relationship based questions and anthropological approaches)	Medium: study dates not specified, though can assess date of data collection knowing this was connected with larger MDP301 study; no theoretical approach articulated for the study	Medium-High: qualitative research within a pilot for a larger trial	High: specifically evaluates experiences of gel use	Medium-High
Montgomery, Catherine M; et al	Re-framing microbicide acceptability: findings from the MDP301 trial	2010	Pro2000 gel	Semi-structured, serial IDIs	Component of MDP 301 phase III randomized trial	South Africa, Zambia, Uganda and Tanzania	Sexually active adult women/trial participants	464	The trial started in October 2005 and completed follow-up in August 2009	emic approach to acceptability	High: all details included	Medium-High: qualitative research within a larger trial setting	High: specific to women's experiences of gel, and their interpretations of use	High
van der Straten, A; et al	High Acceptability of a Vaginal Ring Intended as a Microbicide Delivery Method for HIV Prevention in African Women	2012	Placebo vaginal ring	FGDs	randomized safety and acceptability study (mixed methods)	South Africa and Tanzania	Sexually active adult women/trial participants	48	April 2007 to March 2010	Not specified	Medium-High: no theoretical approach articulated for study	High: qualitative research within a pilot/acceptability study	High: specifically aimed at understanding possible motivations and barriers to use of the ring	High

Montgomery, Elizabeth T; et al	Sharing the trousers: gender roles and relationships in an HIV-prevention trial in Zimbabwe	2012	MIRA diaphragm and replens lubricant	FGDs and IDIs	MIRA Male Involvement Study (ancillary to MIRA trial)	Zimbabwe	Sexually active adult women/trial participants	85	August 2006 to June 2007	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium: specifically looks at gender roles around decision making in the house and around sex, but experiences with diaphragm come through	Medium-High
Okal, Jerry; et al	Secrecy, disclosure and accidental discovery: perspectives of diaphragm users in Mombasa, Kenya	2008	Diaphragm	IDIs and FGDs	prospective study investigating diaphragm continuation rates	Kenya	Sexually active adult women	39	January 2004 - July 2005	None specified	Medium-High: no theoretical approach articulated for study	High: standalone qualitative research	High: specifically aimed at understanding possible motivations and barriers to use of the diaphragm	High
Sahin-Hodoglugil, Nuriye; et al	User experiences and acceptability attributes of the diaphragm and lubricant gel in an HIV prevention trial in southern Africa	2011	MIRA diaphragm and replens lubricant	FGDs	MIRA Trial phase III RCT	Zimbabwe and South Africa	Sexually active adult women/trial participants	105	August 2006 to January 2007	None specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	High: specifically evaluates experiences of diaphragm and gel use	Medium-High
Stadler, Jonathan & Saethre, Eirik	Blockage and flow: intimate experiences of condoms and microbicides in a South African clinical trial	2011	Pro2000 gel	IDIs, FGDs, and participant observation	Qualitative research conducted during MDP301 phase III efficacy trial	South Africa	Sexually active adult women/trial participants	179 women in 401 IDIs, 42 FGDs	Trial was completed in August 2008 and follow up completed in August 2009	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium-High: examined women's interpretation and meanings of condom and gel use; leads to motivations and barriers but not explicitly examining	Medium-High

van der Straten A; et al	Women's Experiences with Oral and Vaginal Pre-Exposure Prophylaxis: The VOICE-C Qualitative Study in Johannesburg, South Africa.	2014	TDF gel and Oral TDF and Truvada	IDIs, serial ethnographic interviews, FGDs, observations	Qualitative sub-study in VOICE phase III randomized clinical trial	South Africa	Sexually active adult women/trial participants	102	July 2010 and August 2012	social-ecological model	High: all details included	High: qualitative sub-study for larger trial	High: specifically examines user experiences of gel and pill use	High
Gafos, Mitzy; et al	The implications of post-coital intravaginal cleansing for the introduction of vaginal microbicides in South Africa	2014	Pro2000 gel	serial ethnographic interviews	Qualitative research conducted during MDP301 phase III efficacy trial	South Africa	Sexually active adult women/trial participants	84	March 2006 to August 2008 with follow-up visits continuing until August 2009	Not specified	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium - explores vaginal hygiene practices within context of gel use	Medium-High
Lees, S	Emergent HIV technology: urban Tanzanian women's narratives of medical research, microbicides and sexuality	2015	Pro2000 gel	IDIs and observations	Qualitative research conducted during MDP301 phase III efficacy trial	Tanzania	Sexually active adult women/trial participants	99	November 2005 to August 2009	None specified (though used anthropological approach)	Medium-High: no theoretical approach articulated for study	Medium-High: qualitative research within a larger trial setting	Medium-High: specifically explores motivations for participating in research, but also includes experiences and interpretations of gel use	Medium-High
Magazi, Busisiwe; et al	Influences on visit retention in clinical trials: insights from qualitative research during the VOICE trial in Johannesburg, South Africa	2014	TDF gel and Oral TDF and Truvada	IDIs and FGDs	Qualitative sub-study in VOICE phase III randomized clinical trial	South Africa	Sexually active adult women/trial participants	102	July 2010 to August 2012	social-ecological model	High: all details included	High: qualitative sub-study for larger trial	High: specifically examines user experiences of gel and pill use	High

Montgomery, Elizabeth T; et al	Male partner influence on women's HIV prevention trial participation and use of pre-exposure prophylaxis: The importance of understanding	2015	TDF gel and Oral TDF and Truvada	IDIs and FGDs	Qualitative sub-study in VOICE phase III randomized clinical trial	South Africa	Sexually active adult women/trial participants	102	July 2010 to August 2012	social-ecological model	High: all details included	High: qualitative sub-study for larger trial	Medium-High: looked more at partnership dynamics than experiences of product use, but influences of dynamics on use is explored	High
Stadler, J; et al	Hidden harms: women's narratives of intimate partner violence in a microbicide trial, South Africa	2014	Pro2000 gel	serial IDIs	Qualitative research conducted during MDP301 phase III efficacy trial	South Africa	Sexually active adult women/trial participants	401 IDIs with 150 women	Not actually specified except "up to 2010" (see other MDP papers)	None specified	Medium: study dates not specified, though can assess date of data collection knowing this was connected with larger MDP301 study; no theoretical approach articulated for the study	Medium-High: qualitative research within a larger trial setting	Medium-High: looked more at partnership dynamics than experiences of product use, but influences of dynamics on use is explored	Medium-High
Van Der Straten, A; et al	Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: The VOICE-C qualitative study in Johannesburg, South Africa	2014	TDF gel and Oral TDF and Truvada	IDIs and FGDs	Qualitative sub-study in VOICE phase III randomized clinical trial	South Africa	Sexually active adult women/trial participants	102	July 2010 to August 2012	social-ecological model	High: all details included	High: qualitative sub-study for larger trial	High: specifically examines user experiences of gel and pill use, and in particular how meanings of ARVs for prevention can become conflated with treatment and being HIV +	High

Table 2. Second and Third order constructs

Third Order Labels	Second Order Constructs	Summary definition (translation) of the 1st and 2nd order constructs	Sources
Sexual Satisfaction	General Sexual Satisfaction	The use of HIV prevention products like the microbicide gel can improve sexual satisfaction within the individual, partner, client, and couple combined.	Gafos et al, 2010; Greene et al, 2010; Montgomery et al, 2010; van der Straten et al, 2012; Okal 2008
	Sexual Performance and Play	Product use can improve performance allowing the user or individual to perform better, be hotter, for her partner, and partners or clients can last longer. There is also the added foreplay of initiating product use (ex. applying the gel).	Guest et al, 2008; Stadler & Saethre, 2011; Montgomery et al, 2010; Stadler et al, 2014; Gafos et al, 2010
	Implications of enhanced satisfaction	Enhanced sexual satisfaction increases trust among some couples, can promote security in the relationship if male partners find their main partners more attractive because of improved sex, and the sense of additional safety from the protection conferred adds to the sexual satisfaction.	Montgomery et al, 2010; van der Straten, et al 2014
	Lubrication and traditional vaginal practices	Previous intravaginal cleansing and insertion practices can be replaced by product use (ex. microbicide), and can improve feeling of sex and feeling of vaginal, making sex more smooth. This more often improves sexual satisfaction, but added wetness can also imply promiscuity in some instances.	Gafos et al, 2010; Greene et al, 2010; Guest 2008; Lees, 2015; Montgomery et al, 2008; Stadler & Saethre, 2011; Montgomery et al, 2010; Sahin-Hodoglugil et al, 2011
Trust	Trust or lack of trust in partner	Product use could be motivated by fear of an unfaithful partner, where they had been and whether they would use a condom. General trust that a partner would use a condom properly was also often missing. In these cases, other HIV prevention products (gel, PrEP, or diaphragm) could confer added protection and peace of mind.	Sahin-Hodoglugil et al, 2011; Kacenek et al, 2012; van der straten et al, 2014; Guest et al, 2008; Kacenek et al, 2010; Sahin-Hodoglugil et al, 2011; Mathenjwa et al, 2012; Lees 1015
	Implications of product use for development and maintenance of trust	Intimacy and creating and maintaining trust are important in relationships where other HIV prevention product use could reaffirm the relationship while condoms carried negative connotations of distrust, denoting infidelity. However, there was sometimes a worry that gels or oral PrEP could promote promiscuity, or at least suggest it.	Okal et al, 2008; van der Straten et al, 2014

	Communication and Enabling Environments	Partner trust of a product was critical, because the trust in the product would translate to trust in a partner as well. Communication and disclosure of product use would improve use of the product, as well as overall communication in the relationship. If not discussed, or if the male partner did not trust the product, there was possibility for arguing and violence.	Montgomery et al, 2008; Stadler & Saethre, 2011; Montgomery et al, 2010, Greene et al, 2010; Montgomery et al, 2012; Montgomery et al, 2014; Montgomery et al, 2008; Kacanek et al, 2012; van der straten et al, 2014; Magazi et al, 2014; Montgomery et al, 2015; Sahin-Hodoglugil et al, 2011; Stadler et al, 2014
Empowerment and Control	Self-esteem and personal agency	Product use had positive effects on personal agency and self-esteem leading women to feel empowered by the ability to decide to use a particular product and that there was something they could use without necessarily needing a male partner's consent. However, in some cases the product could reduce the sense of personal power if it reminded the user of previous trauma.	Sahin-Hodoglugil et al, 2011; Okal et al, 2008; van der Straten et al, 2012; Mathenjwa et al, 2012; Abrahams et al, 2010; van der Straten 2014; Lees 2015; Stadler & Saethre, 2011; Kacanek et al, 2012; Guest et al, 2008; Greene et al, 2010
	Power positioning (Negotiation and control, Product use and engagement in services affects power dynamic)	Male partners could react negatively to women having decision making power over product use, clinic attendance, or even knowledge that they did not possess. This could result in anger or violence in the household.	Stadler et al, 2014; Montgomery et al, 2015; Montgomery et al, 2012
Personal Well-being	Product use promotes health and well-being	The use of HIV prevention products was seen as a deliberate action to promote one's own health and sense of well-being. Products could strengthen the sense of self and empowerment, as well as prevent multiple diseases and improve health issues. The physical experience of side effects could also contribute to the sense of protection from the products. The engagement in health services in connection with HIV prevention product use was also a part of seeing oneself as being healthy and promoting that image to others.	Stadler & Saethre 2011: Montgomery et al, 2010; Magazi et al, 2014; van der straten et al, 2014

	Quality of care as motivation for engaging in healthcare	The quality of care could motivate or demotivate use of HIV prevention products, negative or positive attitudes from health worker staff would transfer to the individual and promote either their sense of good health or negative feelings towards health.	Van der Straten 2014, Magazi 2014
Social Well-being	Perceived implications of use (how I'm seen by others)	People using products can fear what others will think of them as someone who uses HIV prevention products, largely because of an association with promiscuous sexual activity	Okal et al, 2008; Gafos et al, 2010
	Social construction of medication and product use	The use of a medication can symbolise illness for some women and can challenge their understanding of what it means to be healthy.	van der Straten et al, 2014; van der Straten et al, 2014; Montgomery et al, 2015
	Conflation of ARVs for treatment and prevention	Family members, partners or wider community members can mistake use of ART based PrEP, for ART used to treat HIV infection. This can lead to stigmatisation of people believed to be HIV positive	van der Straten et al, 2014; Magazi et al, 2014; Montgomery et al, 2015
	Interaction with normative vaginal practices and beliefs	The use of vaginal microbicides in some settings compliments locally normative vaginal practices in helping to cleanse the vagina prior to, or after, sex. However, the converse was also observed and vaginal microbicides can be rendered less effectiveness by virtue of cultural norms relating to vaginal cleansing immediately after sex.	Gafos et al, 2014; Greene et al, 2014; Behets et al, 2008, Stadler & Saethre, 2011
	The role of outsiders	Many of the product trials or demonstration projects have been led and/or delivered by people perceived as 'outsiders', largely relating to a perception that originate in the Northern Hemisphere.	van der Straten, 2014; Guest et al, 2010; Montgomery et al, 2010; Lees, 2015; Montgomery et al, 2014
Practical Considerations	Accessing and storing medication	Physically getting to the clinic to pick up medication or product refills could prove difficult and was an issue in terms of consistent access. Storing medications was sometimes problematic due to stigma within the household or among friends, where personal privacy was minimal.	Greene et al, 2010; Magazi et al, 2014; Montgomery et al, 2010; van der Straten et al, 2014; Abrahams et al, 2010; Mathenjwa et al, 2012

	Taking and adhering to medication	Strategies for using products, such as gel within a certain time period or pills on a daily regimen, could be interrupted by changes in routines or boredom with use. Perceived or actual side effects were also barriers, as was the need to use multiple products such as condoms and gel when wanting to also prevent other STIs or pregnancy. If product use or associated clinic attendance got in the way of livelihood then product use was also demotivated.	Guest et al, 2010, van der Straten et al, 2014; van der Straten et al, 2014; Montgomery et al, 2012,
	Health service level issues	The health service itself, including waiting times at the clinic, required frequency of visits in relation to livelihoods, and transport and ability to get to the clinic could also cause problems in consistent and continued product use.	Magazi et al, 2014
	Product attributes and acceptability	The ease or difficulty in using a product would directly affect whether a product could be taken up and used. These included need for privacy or washing facilities, whether the product stayed where it was supposed to, ability to transport it inconspicuously, and flexibility around when sex occurred. Pain or irritation with use was also a demotivator. Ability to use covertly was positively regarded, even if rarely done.	Okal et al, 2008; Sahin-Hodoglugil et al, 2011; Montgomery et al, 2012; Greene et al, 2010; Kacanek et al, 2012; van der Straten et al, 2014; Guest et al, 2010; Behets et al, 2008; Gafos et al, 2014; Stadler & Saethre 2011; Guest et al, 2008; Mathenjwa et al, 2012; van der Straten et al, 2012
Efficacy and Risk Reduction	Efficacy for HIV prevention central concern	Whether or not the product can effectively protect them from acquiring HIV was a key concern of women engaged with the products via trials or demonstration projects. Recognition that condoms are not always sufficient drives interest in new product efficacy.	Lees, 2015; Greene et al, 2010; Stadler & Saethre 2011; 2014; van der Straten et al, 2014; Montgomery et al, 2010
	Other (non-HIV) protective effects	While not necessarily accurate in all instances, some female participants expressed beliefs that products could protect them from other STIs or from unwanted pregnancy.	Montgomery et al, 2012; Okal et al, 2008; Mathenjwa et al, 2012; Guest et al, 2008; Behets et al, 2008

	Perceptions around combination prevention	While women may not always be using new technologies in isolation, sometimes a result of concerns for their effectiveness, they were comforted by a feeling that products could provide an additional layer of protection should their primary prevention mechanism (usually condoms) fail.	Sahin-Hodoglugil et al, 2011; Okal, et al, 2008; Guest et al, 2008; Kacenek et al, 2012

Meta-ethnography

Sexual Satisfaction

Constructs of "Sexual Satisfaction" arose in thirteen of the papers we reviewed (27–39). These second-order constructs included: 1) general sexual satisfaction; 2) sexual performance and play; 3) implications of enhanced satisfaction; and 4) effects of vaginal lubrication and traditional vaginal practices. Particularly strong positive feelings were voiced in relation to vaginal microbicide gels (27,28,32), as a result of the "heat", or *kusisha* in isiZulu, created through use (27). This also occurred in relation to diaphragms where many women reported increased vaginal tightness (35), or enhanced stimulation when a partner's penis made contact with the vaginal ring (33). At the same time, women also reported negative reactions from some male partners who found the ring to be obstructive during sex (34).

Particularly striking in its primacy was discussion of how product use could form part of sexual performance and play between couples. Several papers describe how the use of microbicide gels and diaphragms was integrated into sexual foreplay, such as the product insertion performed by the male partner (29,37). Vaginal microbicide use was also associated with increased libido among some women (32,37) and viewed as a means of overcoming sexual problems, particularly in limiting premature ejaculation by male partners (32,36). A perception that the microbicide gel could lead to tightening of the vagina meant that, as described in two papers, male partners would actively request their female partners to use the product to improve the sexual sensation (27,37). In a similar vein, the potential for product use was often seen as facilitating discussion and greater sexual intimacy between partners. Sexual pleasure itself had positive impacts on relationships, improving the performance and play among couples, but also improving the security of the relationship for some women when their husbands stopped seeing other women as a result of improved sexual encounters within the primary relationship (32).

Lubrication played a key role in shaping women's perceptions of microbicide gel use with the majority of papers reporting a positive impact that helped to make sex feel more smooth or comfortable (27–29,31,37,38). Inserting the vaginal microbicide gel mirrored the use of other substances inserted into the vagina to create a pleasing environment for both themselves and their male partner (32).

There are others who insert traditional medicines for her to be enjoyable (during sex) . . . I used to love things that are inserted that make you enjoyable. . . . Now that I am old I don't have that time of going to buy such things. I get help from the gel. (32)

The multiple dimensions of Trust

We found "Trust" to be a particularly strong, complex, and crosscutting construct, either positively or negatively influencing product uptake and use. From various perspectives, trust was either built up or broken down by interactions with partners in relation to product use. Three second-order constructs emerged under this theme including: 1) trust in one's partner; 2) implications of product use for development and maintenance of trust; and 3) communication and enabling environments for trust building. These constructs were identified in 16 of the papers (15,27–38,40–43).

Women's lack of trust in their partners was a strong motivator for use of PrEP, female condoms, microbicide gel, and gel with diaphragm (15,29,30,35). Product use helped ease the fear of possible infections a man might bring home with him, HIV or otherwise, especially when it was difficult to insist upon the use of male condoms within the context of a regular partnership (29,30,35).

Product use also had direct implications for the development and/or maintenance of trust within the couple. In several instances, women reported that bringing an HIV prevention product into the home was negatively seen by partners who felt it implied infidelity on their part or could encourage the woman's promiscuity, thereby impacting their ability to use the products (15,34).

Conversely, for many couples, the microbicide gel did not convey the same level of mistrust that the condom had, making use easier to negotiate (37,38). Communication improved product use, and product use in turn could improve sexual and relationship communication, allowing for new dialogues and trust around sex and intimacy. Disclosure of product use, or lack thereof, also had the potential to influence a woman's standing in her home and her relationship, where use could result in violence or dissolution of the relationship, or help to improve sexual satisfaction and dynamics within a couple (28,32,38,41,43).

Partner support of product use was also a critical factor. Some partners plainly refused to use any prevention products citing mood, general disapproval, or dislike of added wetness from microbicide gel use (15,28,30). However, in many instances, men could also be supportive and

feel they were protected by the product, as well as become involved in supporting their female partner in use, such as providing transport to clinic appointments (28,35,42,43).

Finally, there was an aspect of trust in the product itself, either negative or positive. Negative perceptions often manifested from male partner's disapproval and mistrust in outsiders having influence on sexual relationships or in the efficacy of the product. On the other hand, some couples found that a new product with greater efficacy could actually improve trust and feelings of safety that would motivate use, particularly when they had previously found effective condom use problematic.

> *I like using the diaphragm a lot. My partner likes condoms, but he says they are weak. I also think they are weak [...] [Condoms] burst just like D said. It burst while we were busy [having sex]...So I sometimes use [the condom], but I trust the diaphragm more. (35)*

Empowerment and Control

The interrelated constructs of "Empowerment and Control" were central to women's narratives about how they perceived and used HIV prevention products. Two second-order constructs were identified under this theme: 1) self-esteem and personal agency; and 2) power positioning. These constructs emerged from 14 of the review papers (15,28–30,30,31,33–37,40,41,44).

Some women expressed how products, in particular microbicide gel, vaginal ring, and diaphragm, gave them a sense of ownership and agency over preventing HIV, but also their own bodies and health (33–35). They were able to make the decision to use a product, without a man's consent or involvement. This was especially valuable when women felt that their partners would not necessarily agree or were untrustworthy. Participants suggested that women were responsible for their own health, as this quote notes in relation to the female condom:

> *Men cannot be trusted to act in our best interests. He can wear the condom at the start of the act and then remove it later or he will just tear it. … So we have to take care of ourselves by using condoms. (40)*

In less common contexts, product use can also affect agency, as described in one paper about PEP use within the context of post-rape care. In this paper, successful PEP use after cases of sexual assault was directly related to how the rape was perceived and how the use of PEP

affected the victim on an emotional level (44). Several women reported that the use of PEP reminded them of the rape or made them feel like they were HIV positive, leading to negative associations with the product and demotivated use.

In direct contrast to the generally improved self-agency from product use is the construct of power positioning which emerged as a barrier to product uptake and use. A key concern in this regard was a fear of violence should male partners' discover covert use of the product.

> *'I was scared of the conflict it would cause'; 'if he finds out he is going to be angry'; 'I had seen that he didn't like the gel and I thought if I told him he would fight with me'; 'I think he will fight with me for using the gel with him in secret...' (multiple respondents)(36)*

Women had conflicting feelings about product use. Some felt product use could improve their ability to make choices and negotiate protection, however, this could also pose a threat to men's authority and potentially destabilize the relationship (43).

Personal Well-being

"Personal Well-being" arose as an important construct in how women used and engaged with products. We identified three distinct constructs comprising this theme: 1) product use promoted health and well-being; 2) attributes of product use indicated the power of medication and good health; and 3) quality of care was a motivator for engaging in services and product use. These constructs emerged to varying degrees in five of the review papers (15,32,37,39,42).

Two of the papers (32,37) explored how a microbicide gel gave women a sense of well-being, solved multiple health issues, and prevented other diseases or infections. Indeed the power of the prevention product was seen to have the ability to promote fertility and vaginal cleanliness, clean the blood, and cure ailments (32).

> *As a result of continuous use, my pores are now open. My body is no longer stiff and I don't get tired any more. I am not unsure about my health anymore. Since I started using the gel, I am always energetic like somebody who is using drugs. It has even opened the veins to my kidneys. (37)*

Another paper found that the experience of side effects from ARV-based prevention products encouraged perceptions of the power of the ARVs working in the body to protect the user (15,39).

> *[T]he tablets are also working because they have some reaction on us like some of us have headaches and become nauseous and stuff like that, so you would believe that means that these tablets have a certain possibility of reducing the risk of contracting HIV, you know. (15)*

Interaction with a health service, whether within a trial or actual clinic setting, driven by product use promoted an additional sense of personal well-being in which women could actively look after their own health and be seen by others as 'healthy' (15). Knowledge of one's HIV status with regular check-ups could promote a negative status, leading to continued product use (42).

Additionally, the quality of care during clinic attendance was directly related to motivation for use in two of the papers (15,42). Women noted the importance of staff demonstrating their concern and care for their study participants or clinic clients through educational or one-on-one counselling sessions, in contrast to previous experiences in government public health clinics where staff were often quick to dismiss interests in new products and/or the feelings of their patients (42).

Product use in the social-cultural environment

The construct of "Product use in the social-cultural environment" incorporates four second-order constructs which, combined, represent a significant and sizeable component of the published evidence on the uptake and use of female controlled HIV prevention products (15,27,31,34,35,37–39,42,43,45,46). The four constructs include: 1) perceived implications of use; 2) dominant, setting-specific social construction of medication and product use; 3) conflation of ARVs for prevention and for treatment; and 4) interaction of products with normative vaginal practices and beliefs. Cutting across these constructs is the notion of how women use products within the social-cultural environment and interactions which point to their need or desire to protect their 'social well-being', including their observation of social norms and values.

Many women were concerned that use of vaginal microbicides, the diaphragm, or oral PrEP might suggest to others that they are either promiscuous or identified them as a sex worker

(27,34). Clinic attendance and use of an ARV based technology also caused confusion for the family and friends of some female participants who struggled to distinguish between ARVs for treatment and for prevention (15,42,43). The use of ARVs has become synonymous with HIV infection and, in some instances, sickness (39) and those using ARV-based prevention products were considered to be ill. As such, the social construction of medication and product use encapsulates particular beliefs regarding use of medications. Therefore, a woman's own view of how she sees herself, and how she is seen by others, may be threatened by the use of a technology such as PrEP coming in the form of a tablet (42).

> *Like my family, I explained that I am attending a [PrEP] study but they don't [believe] that I am attending a study, they just thinking I am HIV positive and I am hiding it. (15)*

The impact of beliefs on uptake and use of new products also extend beyond those that relate to HIV stigma. Culturally appropriate or common hygiene practices as they relate to use of prevention products are the focus of several papers within this review (28,37,45,46) and authors highlight the ways in which cleansing practices, in particular, are an important dimension of the social self. Hygiene practices, such as using cleansing products, were reported both as a barrier and an enabler to the effective use and acceptability of vaginal microbicides. Some women found vaginal microbicides highly acceptable given the existing cultural norms around intravaginal insertions for cleansing and preparation for sex (28,32). Partner and social preferences for "dry sex" motivated microbicide use which was seen to have cleansing effects on the vagina, translating into a reduction of STIs and foul-odours previously caused by traditional vaginal cleansing products (37). Interestingly, at least in the South African context, preferences for dry sex seem to actually refer to cleanliness or tightness rather than the desire for a dry vaginal environment, as presented by Stadler and Saethre (37).

The perception and extent of engagement with a biomedical product was also influenced by *who* was delivering the product and whether they were seen as part of the community. Four studies (15,31,32,47) cite concerns relating to the fact that vaginal microbicides, PrEP or the diaphragm were delivered by *muzungu* (white people in Swahili) or people from the northern hemisphere, and a generic mistrust of foreign medications not common in the local setting.

> *So I sometimes think what if what my friends are saying is true, as they say 'what if they are infecting you with AIDS using that gel? (15)*

In several instances it was male partner mistrust of 'outsiders' in their social setting that stood as a significant barrier to uptake and use of the product as they sought to prevent their female partners from engaging in use (43).

Efficacy and Risk Reduction

Constructs of perceived and actual efficacy of prevention products, or the potential for risk reduction, were a significant feature of nine papers (28–30,34,37,40,41,45) and an implicit dimension of three (31,32,39). Three constructs identified among these papers were 1) efficacy for HIV prevention as a central concern; 2) other (non-HIV) protective effects; and 3) perceptions around combination prevention.

The fear of infection was a dominant feature in participants' narratives (28,31) as was the hope that new products may succeed in stemming the epidemic where condoms have been insufficient (37). In several studies, women said that sex was more enjoyable when they felt protected from HIV, as described in Guest et al:

> *It is the diaphragm and gel that made us enjoy sex more because there is no virus that goes inside me or penetrates me. I don't know what he is doing in my absence, and he doesn't know what I am doing in his absence so we are safe when we are using the diaphragm. (29)*

Female participants were comforted by the additional protection that new prevention products offered. While they may maintain a desire to utilise male condoms for many sexual encounters (e.g. to prevent pregnancy or other STIs), it was felt that the diaphragm (34,35) or vaginal microbicides (29) could provide an additional layer of protection from acquiring HIV.

> *I feel free when the diaphragm inside me in this 6 hours I do simply know that even if it has happened that a condom burst, no HIV will be passed on to me. It will go back. (35)*

The preference for use of more than one product at a time affording multiple layers of protection was not uniform. Kacanek et al (2010) highlight the reluctance of women in their study to use both the diaphragm and condoms simultaneously. However, women did acknowledge that this was partly born from a desire to understand the effectiveness of the diaphragm as a preventative HIV transmission method in isolation.

For female condoms and the diaphragm, women articulated their belief, and feelings of comfort, that these methods could also protect them from other STIs and unwanted pregnancy (29,34,40,41,45). The female condom was particularly favoured by women who had experienced problems with hormonal contraceptive methods (40).

Practical Considerations

Four second-order constructs emerged within the third order construct of "Practical Considerations". These included: 1) accessing and storing products, 2) product attributes and acceptability, 3) ability to effectively take or use the product, and 4) issues relating directly to health services. These constructs were identified in 17 of the papers (15,28–30,32–35,37,39,40,42,44–47).

While all of the studies included in this review report data on actual use of products in contexts where the products were provided for research purposes, either in trials or clinic settings, issues around access to the products still arose. This was directly related to women's ability to get to the clinic for refills in between scheduled visits. In some cases women just waited for the their next appointment rather than making an extra trip, or were away from home due to family obligations (28,42).

Storing the products could also pose problems in settings where there is little privacy in the home and women feared accidental discovery and potentially negative reactions from household members or partners (15,32). Some women used the discovery of a product as a means to establish health status and pride around use:

> *At first I was putting [the tablets] inside my bag and then I took them out of it and put them inside my wardrobe but then one of my friends opened my wardrobe. Because she saw that I was taking the tablets and she didn't understand why I was taking the tablets even my partner didn't understand why I was taking the tablets. So I put the tablets in open field so that they could understand that I was taking the tablets for the study and it's not that I was sick or anything like that. (15)*

Attributes of the products themselves could directly influence the ability to use them. With regard to the diaphragm, users found that it could be problematic to insert or remove it without privacy or clean facilities in which to wash themselves and the product. Some women found it painful at first to use, while others appreciated the small size and that it was inconspicuous enough to fit in a handbag or in a pocket (34,35). The long-acting attribute of

the vaginal ring contributed to a feeling of flexibility when sex occurred, as well as constant protection in case of rape (15).

Vaginal lubrication practices also arose under this third order construct from the practical perspective. After using microbicide gel, women articulated that the use of traditional lubricants was less preferred owing to their ability to cause foul-smelling odours, whereas the microbicide gel or the female condom had built-in, clean lubrication which was a strong motivator for use (28). This built-in lubrication would also prevent pain and tearing of condoms or vaginal tissues, as well as dryness, which can occur during longer sexual encounters and as such was preferable to male condoms (29,32,37). The vaginal ring could bring added pleasure to sex as well where the ring itself would add stimulation to the male partner (40).

Other papers presented discussions of traditional or conventional vaginal practices and how they might affect the practical and effective use of products (37,45,46). Women spoke of the "dirt" (or pollution resulting from perceived accumulation of semen, menstrual blood, and lubricants), either their partner's or their own, which could get trapped in their vaginas after sex because of product use (37,46). However, the rinsing of a vaginal microbicide gel or diaphragm within an hour after vaginal intercourse could significantly negate its effectiveness. This issue was amplified for female sex workers who felt a need to cleanse their vagina between clients (45,46). Interestingly, some women felt that using the newer products actually made them feel cleaner, thus reducing cleansing practices and motivating use.

Side effects, whether real or perceived, were a critical influence on continued use of a product. Women stated they would use products providing there were no visible side effects which could alert friends, family, or partners to their use and potentially stigmatise them as being HIV positive (15). Women expressed fear of using products due to potential or experienced side effects (15,33,39), while others were able to quickly overcome the side effects and felt happy to use the product (28). Lack of side effects as experienced with the female condom was a big motivator for use, especially for those women who had experienced them with other products.

An additional practical consideration centres on the consciousness required for consistent and correct pill taking, in particular related to oral PrEP. Some women had difficulty remembering to use the product, such as in the case of oral PrEP, when they were intoxicated, "feeling bored or lazy, on the go", or just not used to having to take a pill every day (15,28).

Finally, issues with health services, even in trial settings, were also factors influencing product use. Waiting times at the clinic would cause women not to attend and pick up their products, as did availability of and ability to get transport, and family, community, or work obligations which disrupted clinic attendance (42).

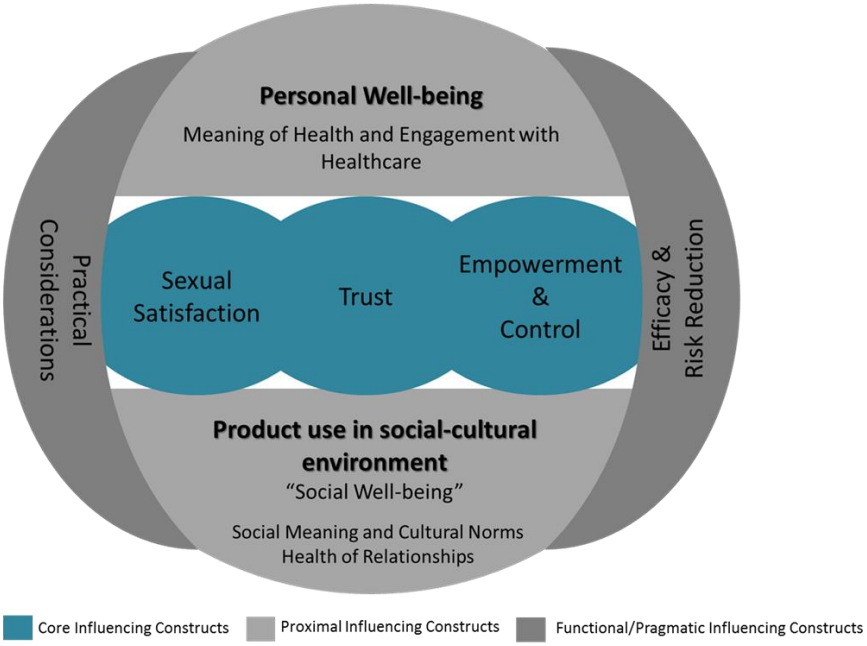
2.4.5 Discussion

The analysis and synthesis of the data included in this review reveal nuanced personal, relational, social and cultural factors that women perceive and attempt to manage as they consider the uptake and use of biomedical HIV prevention products. The factors are far from binary, in that a given factor can act as either a motivator or deterrent to uptake and use depending on the individual context. Our analysis led us to identify seven third-order constructs. Figure 3 illustrates how the third order constructs tend to be situated in terms of primacy to the decision making process to take up and use HIV prevention products, and how they can influence each other in this process.

In this manner, the centrality of “Sexual Satisfaction”, “Trust” and “Empowerment & Control” are emphasised among those constructs that appear more proximal or those that are functional or pragmatic, but which still play a role in product uptake and use. The inter-relationality of these constructs, illustrated by the overlapping circles in the centre of the framework which also connect with the other shapes in Figure 3, is as important as the individual constructs themselves, as no one construct can be isolated and addressed without acknowledging the others. In the remainder of this section we use this framework as the basis for discussing the broader context of the constructs, their meaning and potential impact for policy and programming.

Figure 3. Conceptual framework of third order constructs influencing HIV prevention product decision-making for uptake and use among women in SSA.

Figure 3. Conceptual framework of third order constructs influencing HIV prevention product decision-making for uptake and use among women in SSA.



Core influencing constructs

Improved sexual satisfaction emerged as one of the strongest motivators for using a particular product, especially in relation to vaginal microbicides and the diaphragm. However, this construct was typically positioned within a partnership where trust and empowerment mediated (or were mediated by) enhanced sexual pleasure. Several authors highlighted how the mere fact that sexual satisfaction for both partners plays such a key role in broader relationship satisfaction, and that in many respects vaginal microbicides or diaphragm use help to enhance sexual pleasure, means that this dimension of the product is central to their uptake and use (29,32).

Improved sexual satisfaction in a relationship can directly lead to improved security between a couple, where a husband may stop seeing other women and the main partnership therefore becomes strengthened (32). Product attributes themselves can also contribute to trust, or lack thereof, in a given product. For instance, the added wetness from a microbicide gel could denote infidelity in the eyes of a male partner (28,36), especially in contexts where traditional preferences derived from social norms are for dryer sex. This connotation of lack of fidelity generates a lack of trust and ultimately demotivated use of the product.

We found that many authors approached their research from the perspective of empowerment, or control over prevention choices. Women across the research expressed

how having something that was theirs and/or their choice was important and empowering, but it was not necessarily the primary motivation for use. This is significant to note in the context of a global PrEP and vaginal microbicides discourse that often emphasises empowerment of women as a key component of such products (48–50). While this review demonstrates that empowerment and control issues still play an important role in the decision to use a new technology, they do not necessarily feature as the primary factor in women's' thinking and must be considered within individual contexts.

Empowerment could actually be diminished if a partner discovered covert use of a product and became angry or violent, and fear of these reactions led women either to openly disclose or discuss use with a partner, or stop use altogether. Some women found that empowerment through building trust with their partner and strengthening the relationship through open communication was a positive by-product of introducing new prevention options into the mix.

Proximal influencing constructs

Product use in the social-cultural environment consists of multiple factors pertaining to interactions between women and their communities, and the social norms generated around traditional practices and beliefs, denoting women's sense of 'social well-being'.

Our analysis revealed the importance to women of meeting both cultural norms and expectations of vaginal dryness (31) as well as vaginal cleansing (32). This is where women carefully consider how vaginal microbicide use might impact on good health and the "vaginal environment" (32), which directly relates to perceptions of well-being in the social-cultural environment as well as sexual satisfaction within the relationship. Several authors suggest that in countries or areas where intravaginal insertion prior to sex (e.g. to tighten or dry the vagina) is commonplace, acceptability of vaginal microbicides – and, therefore, uptake and use – may be higher than in areas where such practices are less common (28,32).

The construct of personal well-being speaks to the feelings women had about the impact of products on their health more broadly. Use of products meant not only a continuous process of engagement with healthcare services, but also a general sense of health and cleanliness. A further key dimension of this construct was how others might see women as 'healthy' by virtue of their on-going healthcare engagement. This observation actually sits in contrast with other findings described in some results that suggest women may be the victims of stigma or

discrimination if others come to believe they are accessing HIV services because they are sick, conflating services for prevention with those for (HIV positive) treatment.

Functional & pragmatic influencing constructs

Inherent to the construct of efficacy and risk reduction is the process of decision-making. Women will engage in balancing the potential risk of HIV with the risk to trust her partner, or the risk to intimacy within a partnership that could be threatened by use of HIV prevention products. Products that pose added benefits from product attributes, such as clean lubrication from the female condom or microbicide gel, could outweigh potential issues around distrust or scepticism around product use.

Several authors stressed that the efficacy of the technology in preventing the transmission of HIV was absolutely central to its perceived acceptability (28,29,32), as well as its uptake and use. However, we found that sometimes beliefs about a certain product was as, or more powerful than the reality. For example, the belief that a product could prevent more than HIV, that it could 'cleanse the blood' or prevent other diseases because of how it made the person feel when using or taking it, was a strong motivation for use. Similarly, belief that a product was extremely efficacious as a result of experiencing side effects or a feeling of empowerment promoted continued use.

In order to make effective use of the products women need to be able to store, be able to confidently use, and have barrier-free access to healthcare services. Products must also be developed or formulated in such a way as to be acceptable to women wanting to use them in the medium or longer term. Vaginal microbicides and the diaphragm, in particular, can be difficult for women to insert in adequate time prior to sex and concern was also expressed that their use may interfere with traditional vaginal hygiene practices.

Further reflections on these findings

Since the time that this review was conducted, additional qualitative evidence on perceptions of female-initiated and controlled HIV prevention products or interventions has emerged, particularly from trial research around oral PrEP. The HPTN/ADAPT study (51), which compared daily to intermittent dosing of oral PrEP in a phase II clinical trial setting, has recently published qualitative research which further supports and develops the findings in this paper. In this study, they found nuanced motivations and barriers linked to perceptions of safety taking PrEP, trust in what PrEP really was and whether it really worked, whether its

providers were worthy of trust, and a sense of community commitment and dedication with regards to adopting (or not) the PrEP intervention. The insights related to trust, or lack thereof, in oral PrEP have been further supported by findings from the VOICE D study (a sub-study of the main VOICE study on preferences and adherence) where women expressed concerns around safety and efficacy of PrEP as well as similar community perceptions which affected their own thinking (52,53). As more data continue to emerge from ongoing trial research as well as the early PrEP implementation studies which will start to publish results, perceptions which might create product-specific stigma, distrust, and aversion will be important to consider when designing messaging and education campaigns. Additionally, it will be important to 'arm' health workers and clinicians providing PrEP will accurate information and careful training to be able to address rumours head on.

In this review, oral PrEP was discussed less than other products (such as microbicide gels or the ring) with regard to sexual satisfaction, largely because it lacked tangible attributes that could contribute to improved pleasure. However, social marketing campaigns have evolved since this review was conducted that capitalise on the ability of PrEP to remove some of the fear around sex which can then lead to improve satisfaction or pleasure (54). PrEP and other HIV prevention products may present a new opportunity to develop discourse around sexual pleasure even in places traditionally closed to these notions.

Vaginal practices played a key role in much of the research surrounding vaginal products such as the gel and the ring with regards to traditions and habits of women. Interestingly, the notion of "dry sex" was revealed in some of the literature to be less about having a dry vaginal environment, but rather more about the cleanliness of the vagina and "hotness" of the sex. Regular clinic visits allowed women to be more consistently free of STIs, and use of the gel provided clean lubrication, which most women and their male partners enjoyed. If there is to be continued pursuit of vaginal HIV prevention products, this line of enquiry may benefit from further investigation.

Adherence, or the burden of adhering to a specific HIV prevention product regimen, was not a theme that emerged as prominently as others in this review. However more evidence has emerged recently about levels of adherence required to ensure efficacy, and findings from qualitative research may help to shed light on where issues lie in maintaining consistent use. Oral PrEP in particular requires high levels of adherence to confer adequate protection,

particularly among women (55,56). This will also be an important consideration for large-scale PrEP implementation as well as for development of new HIV prevention products.

Finally, as the research included in this review comes from studies where participants received some form of financial reimbursement for participation, and the products were provided free of charge, it is not possible to determine how perceptions of use may differ in a context where this was not the case. Future research could examine this further, and potentially use the findings from this paper to develop surveys to also quantitatively assess motivations and barriers to use in more 'real-world' settings.

Strengths & Limitations

This is the first review paper of its kind to aggregate data from across a large population of women, from multiple sub-Saharan African countries, relating to a range of female controlled HIV prevention products. In doing so we have documented the key themes or issues that can influence their uptake and use and how these overlap according to context and the specific technology. The systematic review involved searches in all languages, double screening and double extraction of relevant data from each paper. Our explicit focus on studies where the product of interest was available, rather than simply the object of theoretical discussion with women, helps to ensure the findings are grounded in personal experience.

The papers in this review, however, included mostly data gathered in the context of clinical trials where products were freely given and participants were usually reimbursed for costs associated with participation (such as transport to and from clinics). The unique environment and provision of wrap-around counselling and treatment services does not often mirror the real-world implementation of new products. Nevertheless, regardless of this, the themes that emerged were common across a wide range of countries, implementation contexts (including clinical trial and implementation studies), and cultural settings, as well as across the products themselves, suggesting a relatively robust body of evidence. One crucial consideration, however, relates to the construct of product use in the social cultural-environment, where social norms are seen to influence uptake and use of products. As those products found to be efficacious are rolled out into countries and communities, the extent to which their use is 'normative' will also change. This would certainly have affected the data included in this review as none of the products had been in the field long enough for use to have been normalised. It is also important to note that while this review of evidence only included

perspectives from women, it is clear that the perspectives of men influence women's choices, decision making, and effective use.

A further limitation of this analysis is the limited nature of published qualitative research. Often it is required, for word length purposes, to condense detailed findings to a few sentences that capture their essence. Understandably, the papers included in this review will have focused on certain viewpoints, whereas there may be many more data providing additional nuance, which could contribute valuable insight.

Finally, while it is a strength of this review that we have synthesized qualitative data from across research contexts, it is also somewhat of a limitation that the contexts were not more diverse and include more pure implementation research studies. The body of evidence for understanding the motivations and barriers to uptake and use of female-initiated HIV prevention products can be further strengthened by more lessons learned and documented from the field.

2.4.6 Conclusions

This is an exciting time in HIV prevention as new biomedical products are developed and systems put in place to ensure their effective rollout. Health systems, structural and direct contact level interventions relating to new products need to take into account more than just superficial notions of acceptability. Instead, they should focus on a holistic approach including: aspects of how a product can protect a partnership (in terms of physical and emotional health); an awareness of the significance of sexual satisfaction and enjoyment; an understanding of the social and cultural norms influencing product use; and include efforts to tackle the continuing stigma associated with HIV. Structural and individual level interventions aiming to improve uptake and use of those products already available have tended to focus on practical issues (e.g. access to products and services, ability to use and store products safely, access to hygienic facilities). These may be perceived as the 'low hanging fruit' as issues that lend themselves to immediate intervention, but they do not necessarily reflect those concerns that are most central to effective uptake and sustained use of the product from the perspective of the user. While the reduction of transmission risk is essential for the use of any of these products, and has justifiably been the focus of international scientific attention, this is not often the key determining feature of use. Formative research conducted in each setting prior to the roll out of new product-based interventions will help to ensure that communications and educational materials are aligned to the local cultural and social norms,

and take account of both personal concerns and personal values in safer, and enjoyable, sexual practice.

Declarations

Ethics approval and consent to participate

No ethics approvals were sought for this work as it comprises a secondary analysis of published data. As such, individual participant consent was also not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All of the data included in this paper are available through the individual publications.

Competing interests

The authors have no conflicts of or competing interests to declare.

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Author Contributions

RE conceptualized the study. RE, AB, CJ, HL contributed to overall design. RE conducted full abstract and title review for rounds 1 and 2 searches, CJ was second reviewer for round 1, and AB was second reviewer for round 2. RE, AB, and CJ reviewed full texts for inclusion. HL and JS read all papers and contributed to analysis framework constructed by RE, CJ, and AB. RE and AB drafted manuscript with contributions from all authors. All authors have given approval for the version to be published.

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3.0 Chapter 3: Methods employed and lessons learned from designing a PrEP intervention for FSWs in South Africa

3.1. Introduction

Chapter 3 addresses the research question associated with PhD Objective 2: *What are the practical and contextual factors which might affect the uptake and use of PrEP among FSWs in South Africa?* This question was addressed through the experience of conducting formative research to develop interventions to be implemented and evaluated in the TAPS Demonstration Project. While this PhD focuses on PrEP, the TAPS project included both PrEP for HIV-negative women and early ART for HIV-positive women. As discussed in the paper, this is a direct result of demand voiced during consultations and discussions with sex worker organizations and sex workers themselves. Since these two interventions were combined and this paper was written both for sharing learning from the project with a broader audience as well as for this PhD, it was not possible to separate the two interventions into different papers. In addition, PrEP cannot be implemented in a vacuum, separate from other clinical and behavioural interventions, therefore it was important to take into account the wider delivery environment as well as the sex work context. Indeed, the learning related to the design of both interventions overlapped and pointed to many synergies which could be capitalised upon in the project. One in particular, which develops throughout this PhD, is the notion of social support among HIV-negative and positive women who are all taking pills and often motivated by similar reasoning. This will be explored in more depth in Chapters 4 and 6.

The paper contained in this chapter describes the method of employing an inductive approach based on the principles of grounded theory (1) to choose methods and make decisions concerning intervention design due to the broad original scope of PrEP and early ART implementation considerations. This methodological approach was used given the many unknowns regarding PrEP implementation in general, and for FSWs in particular. A range of methods were considered at the outset (formal surveys, focus group discussions, interviews, site assessments, consultations), however, it was more appropriate to let the findings elicited after each step dictate the subsequent methods rather than employ a fixed plan from the outset. This grounded approach allowed for broad exploration of factors which might either support or detract from the interventions. These factors are situated within the spheres of the MSEM pertaining to the interactions with HIV prevention across individual, social, community, policy and epidemic contexts. This work addresses issues around applicability of PrEP for FSWs, where relevance and responsiveness are critical in designing the intervention.

The approach and decisions made relied heavily on systematic and extensive engagement with stakeholders and experiences during outreach in the field accompanying the existing Sex Worker Programme staff during health promotion and clinical services. Working through the existing programme was essential in order to build the TAPS interventions into relevant, or applicable, options for FSWs to take up and use. This formative research focused primarily on the applicable or practical components of intervention design and delivery – namely where, in which contexts, how, and when the interventions should be offered. The final piece of the formative research took the form of focus group discussions with potential end-users which will be described in the following chapter. The strength of this research is the systematic way in which it was undertaken, at the same time relying on a grounded approach to allow for the data to drive the decisions. Formative research is almost always undertaken before programme implementation, but rarely reported in detail.

This paper was submitted for publication to BMJ Open in July 2017 and is awaiting an editorial decision.

3.2. References

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SECTION A – Student Details

Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS Med
Please list the paper's authors in the intended authorship order:	Robyn Eakle, Nyaradzo Mutanha, Judie Mbogua, Maria Sibanyoni, Adam Bourne, Gabriela Gomez, Francois Venter, Helen Rees
Stage of publication	Undergoing revision

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I partnered with Dr Gabriela Gomez, Prof Francois Venter, and Prof Helen Rees on the design of the research. I am Co-Principal Investigator on the study and project lead. I led the development of most of the data collection tools. Dr. Gomez led the statistical

	analysis with support from me. I conducted all of the qualitative analysis. I lead the drafting of the manuscript.

Student Signature: [redacted] Date: 5 October 2017

Supervisor Signature: [redacted] Date: 5 October 2017

3.3. Designing PrEP and early HIV treatment interventions for implementation among female sex workers in South Africa: developing and learning from a formative research process

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Word count: 5,446
Number of figures/tables: 1
References: 25

Key words: HIV prevention, biomedical prevention products, pre-exposure prophylaxis (PrEP), sex work, formative research

3.3.1. Abstract

Objectives

This paper examines how an inductive approach, based on the principles of grounded theory, to formative research influenced the design and execution of oral pre-exposure prophylaxis (PrEP) and early antiretroviral (ART) interventions for female sex workers (FSWs) in South Africa.

Setting

The formative research was carried out in a variety of locations as dictated by the inductive approach. These included five sites in and around sex worker clinics, and at stakeholder offices.

Participants

Participants in this research included stakeholders, experts in the field, and FSWs. Since this was an evolving, inductive approach to research, numbers of participants were not always tabulated except in the case of focus group discussions (FGDs).

Results

Results consisted of methods chosen and subsequent data. Five chosen methods were: 1) stakeholder consultations launching and evolving the research; 2) engagement with FSW communities and working environments including hotspot mapping and clinic interactions; 3) site feasibility assessments for site selection; 4) supportive structures development for retention and adherence; 5) FGDs conducted with FSWs to explore specifics of acceptability. This process identified implementation barriers, opportunities, and research gaps critical to intervention design. Two sites were selected in Johannesburg and Pretoria, out of five considered. The contexts of the two urban sites varied, necessitating adjustments to intervention implementation.

Conclusions

Using an inductive approach allowed for a wide range of perspectives, defining population needs and how to best reach them. This research illustrated how similar sex work environments can vary and how implementation of interventions may not be uniform across contexts. Lessons learned in details could assist in future project designs and implementation of new interventions where feasibility, social and cultural factors affecting acceptability must be considered.

Strengths and Limitations

- This formative research process drew on principles of grounded theory allowing for an inductive, iterative approach to drive the selection of the most appropriate methods for gathering a broad spectrum of data aimed at intervention design.
- Five components were selected through the research process, providing an array of data for decision making and intervention design.
- This was a systematic approach in five known sex worker sites and final sites were chosen for their nearer uniformity than for diversity; results may not translate beyond this study, however lessons learned will be applicable.

3.3.2. Introduction

Several guidance documents highlight the need for formative research both when preparing for larger studies and to design the implementation of new public health HIV interventions (1,2). Formative research includes the assessment of feasibility, reach, acceptability, and need of populations to strengthen planned uptake and use of interventions. In particular, formative research aims to ensure the capacity for physical implementation and responsiveness to cultural, social, economic and physical environments (3–5). However, this phase of work is frequently not reported and important lessons learned may be lost. This paper describes the detailed decision making and conduct of formative research undertaken to design two new HIV prevention and treatment interventions delivered to female sex workers in a demonstration project in South Africa.

Oral pre-exposure prophylaxis (PrEP) using antiretroviral (ARV) drugs given to an HIV-negative individual to prevent HIV infection, has been shown to be efficacious in multiple clinical trials (6). In additional, HIV treatment can be given to HIV-positive people as soon as they are diagnosed, and together with oral PrEP, is now the standard of care recommended in 2015 by the World Health Organization (WHO) (7).

Demonstration projects were recommended by the WHO in 2013 to generate evidence to answer implementation questions around feasibility and acceptability of oral PrEP (8). The call prioritised research for key populations such as sex workers, who have been shown by modelling to be ideal candidates for PrEP, especially in combination with early antiretroviral (ART) treatment for HIV-positive people (9–11). In the previous decade, HIV prevalence among female sex workers in South Africa was found to be between 46% and 69% (12–14), with recent research estimating a prevalence of 72% in the greater Johannesburg area (15).

This paper examines and illustrates how a comprehensive and inductive approach to formative research based on grounded theory (16) informed the design and execution of oral PrEP and early antiretroviral (ART) interventions for female sex workers in South Africa as part of the TAPS (Treatment And Prevention for Sex workers) Demonstration Project. The purpose of TAPS was to demonstrate how these two interventions could be implemented among female sex workers, and inform national rollout. We explore the approach and process undertaken to define and carry out the formative research, describe how the results informed the overall design of the oral PrEP and early ART interventions for TAPS, and reflect on challenges and successes encountered during the process.

3.3.3. Methods

Formative research can include an array of methods depending on the final desired outcomes. For the design of interventions, formative research will include exploring feasibility of supportive structures and logistics for physical delivery of the intervention, as well as exploring the acceptability among populations in different contexts (2).

The overall aims of the larger TAPS Demonstration Project were to explore whether FSWs will take up early ART or PrEP, whether the service delivery mechanism is capable of handling the increase in resource needs that might be required, and what the implications of the implementation of these interventions might be, including overall costs should the interventions be scaled up (17). TAPS is part of the Wits RHI Sex Worker Programme (SWP), a comprehensive health and well-being programme for sex workers running for over 20 years in Johannesburg and other provinces in South Africa (18).

While TAPS itself aimed to answer questions of feasibility and acceptability in the actual delivery of PrEP and early ART for female sex workers, the formative research began with foundational concepts of feasibility and acceptability in order to design interventions which could then be evaluated. These concepts addressed questions including: whether there was initial support from stakeholders to test the implementation of PrEP and early ART; where could the interventions be delivered, how, and by whom; how to engage with female sex workers; what was needed to generate demand; what structures should be included to support delivery; and how did women conceive of acceptability as users of the interventions?

The formative research was conducted between August 2013 and March 2015. An inductive approach was employed based on the principles of grounded theory (16), where lessons emerging from the data at each step in the research process dictated decisions and subsequent steps. A grounded approach was chosen given the wide original scope required to consider a large range of logistical possibilities (e.g. site locations, adherence support structures) for the design and implementation of the interventions.

Decision making about which methods, sites, and stakeholders with whom to engage at each step was guided by feedback from consultations and discussions. Principles from the Good Participatory Practice Guidelines (GPP) developed by UNAIDS and AVAC were also followed, promoting multi-level stakeholder engagement as a core component of research (1). In line with these guidelines, a range of stakeholders were engaged, including sex workers, sex work

related organizations, and the Department of Health (DoH). Community mobilization and outreach served to develop awareness around the interventions and generate demand led by peer educators who were current sex workers. Site assessments were conducted as part of feasibility which included site visits, and took into account findings from the community engagement and 'hot spot' mapping activities (identifying areas in which multiple sex workers operate). Additionally, focus group discussions (FGDs) were held with female sex workers at the final selected sites. Since the development of the methods for this process represents results in and of themselves, the specifics of how activities were chosen, why, and what was learned, are detailed as part of the results.

These activities eventually fell into five core methods: consultations, community engagement and mapping in the field, site assessments, participatory development of supportive structures and messaging, and FDGs. These methods generated three primary sources of data which informed the design of the interventions: 1) recorded minutes and reports of meetings with stakeholders; 2) field notes from engaging with sex worker communities and the environments within which they work, the process of hotspot mapping, experiences at potential clinic sites, and through the development of supportive structures; and, 3) transcripts of FGDs. Outcomes included the final design of the intervention incorporating perspectives of stakeholders gathered from the data, as well as relevant data collection and monitoring tools and supportive structures. These data were collected by a combination of researchers, peer educators, and clinical staff.

Data analysis

Data were continuously collected and analysed based on the inductive approach over 18 months. Field notes, meeting notes, written reports, and FGD transcripts, were reviewed as activities occurred to identify key themes for further exploration and to define next steps, such as whether to disqualify a site due to low accessibility of the population or where to spend more time on community mobilization, education, and hotspot mapping. Site selection and staff recruitment represented the end of the first major phase of formative research. Community mobilization was then focused at the selected sites where testing of messaging, development of supportive systems, and development and testing of potential data collection tools continued led by clinic staff, peer educators, and potential end users.

FGDs were conducted at each of the final selected sites in multiple languages to suit the participants and analysed following principles of thematic analysis (19), concentrating on

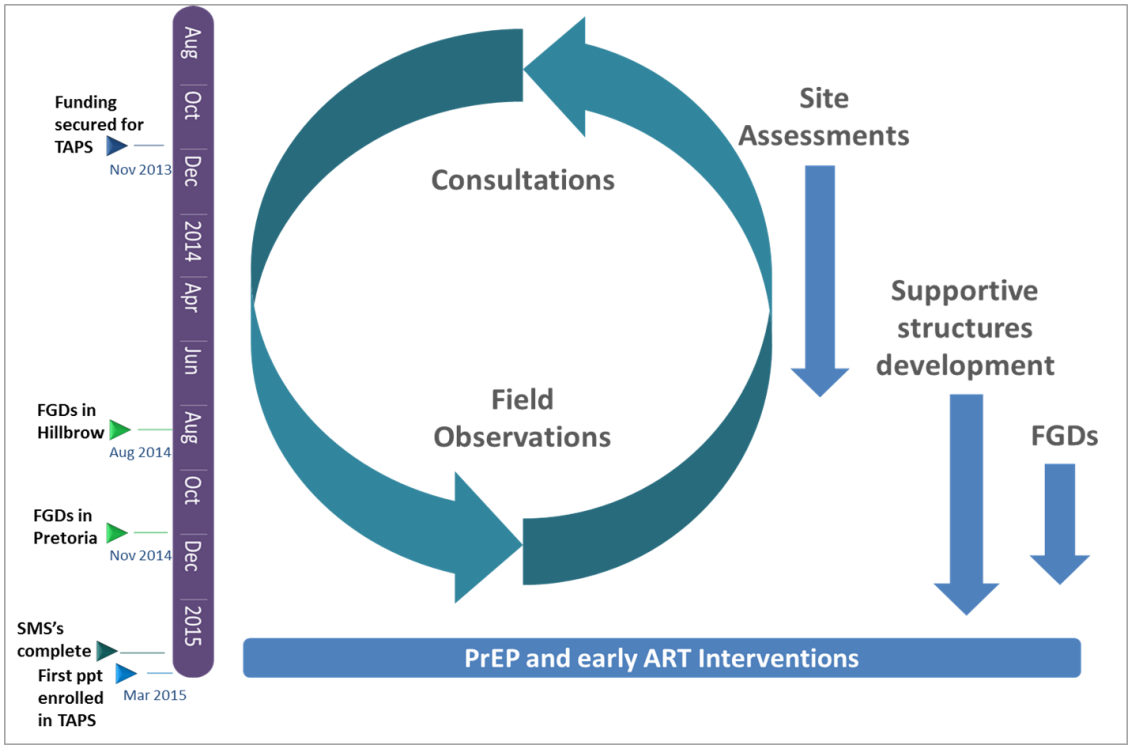
themes originating from the FGD guides and those emerging from the discussions. Further details of the methods and results from the FGDs are presented in a companion paper (20).

3.3.4. Results

Results are presented in five sections according to the chosen methods as products of the grounded approach. Sections include how and why methods were chosen and undertaken, and lessons learned influencing the design and execution of the interventions.

The five methods were: 1) stakeholder consultations both launching and iteratively progressing the research with stakeholder perspectives; 2) community engagement in the field with sex workers and the environments within which they work including hotspot mapping and experiences at potential clinic sites; 3) site assessments to determine feasibility of delivering the interventions in given sites; 4) development of supportive structures to encourage retention and intervention adherence; 5) FGDs conducted with potential end-users to explore specifics of acceptability. A diagram of the five methods and the timeline during which they occurred is shown in Figure 1, illustrating how some activities were continuous and others discrete.

Figure 1. The formative research process and timeline to design the PrEP and early ART interventions for TAPS.



Abbreviations: ppts = participants; SMS = Short Message System; FGDs = Focus Group Discussions

Stakeholder Consultations

Research began with this activity in order to ascertain stakeholder knowledge of and attitudes towards PrEP and early ART, as well as attitudes towards sex workers, which denoted initial levels of acceptability for the interventions in this population. We conducted three community consultations in 2013 with a total of 81 attendees from sex worker communities and partner organizations in Hillbrow and Ngodwana, where a new sex worker clinic was in the initiation phase. Additionally, an international consultation of 38 attendees was held in Hillbrow in 2013 and included representatives from sex work communities and organizations, funders, UNAIDS and WHO (21). These consultations allowed for mapping of organizations and individuals to be included in future consultations and phases of formative research.

Smaller meetings were held with local DoH representatives in Johannesburg, Mpumalanga, Phongolo, and Pretoria to develop partnerships and support agreements for the TAPS project. Updates on, and engagement with, the plans for the TAPS interventions continued at quarterly and other scheduled meetings with local DoH and partners. Parallel meetings were also held with National DoH and the South African National AIDS Council (SANAC).

Feedback from the consultations pointed to varying degrees of support depending on local capacity to take on new interventions and scepticism towards the interventions, and particularly PrEP. Stakeholders affirmed that implementing PrEP and early ART together would promote synergistic delivery, as well as potentially normalise the use of ARVs in providing options to both HIV-negative and positive sex workers. However, concerns were voiced about adherence to PrEP (and sometimes early ART), as well as the potential for reduction in condom use, increases in risk of resistance to ARVs, and burden on scarce resources. These concerns indicated where special attention should be focused, such as providing evidence about possible resistance to PrEP and strategies for and the philosophy around supporting adherence and condom use, both in early messaging and education for sex workers, implementing and policy partners, as well as where to focus messaging and monitoring when implementing the interventions in TAPS.

Sex workers at each potential site, driven largely by peer educators, helped to identify community organizations to engage for additional perspectives. Stakeholder engagement, both formal and informal, was tracked using an engagement tracking tool (22) developed by the HIV prevention advocacy group, AVAC. According to the data recorded in the tool, at least

20 meetings occurred during this time; however it is not possible to definitively quantify all of the contact points given that many interactions occurred on an ad hoc basis.

Finally, consultations were also used to identify potential community advisory board (CAB) members. Meetings were held with individuals expressing interest in participation to inform them about the study and the CAB. These discussions continued until a CAB with up to 12 members was established. The CAB incorporated representatives from the local police force, sex worker advocacy organizations, sex workers themselves, and religious organizations. The CAB became both a result of the formative research and another source of consultation. The CAB was also a supportive structure for the interventions as members took it upon themselves to help spread knowledge of the interventions and the TAPS project, as well as lobby for expansion of the interventions to more sites, populations, and organizations.

Community Engagement and Mapping

Data were also collected through community mobilization activities, accruing organically in scope and number, as discussions and interactions within the communities pointed to additional contacts for engagement. Each point of contact presented opportunities for new consultations and/or locations to conduct outreach. Feedback from the community about potentially adding PrEP and early treatment as new HIV prevention and treatment options was collected during peer and clinical staff outreach and workshops, which also aimed to generate demand for the interventions in the potential demonstration project site communities.

Outreach is a specific set of activities in the sex worker service delivery field undertaken to educate clients about health, promote condom use, and provide a spectrum of services from HIV testing and counselling to full clinical services in mobile units in locations accessible to the population (23). Staff and peer educators from the SWP, in collaboration with TAPS staff and researchers, conducted outreach as a team to probe the local sex worker populations for any knowledge or perceptions of PrEP and early ART, as well as start to introduce related information. This outreach occurred as part of existing programming consisting of health talks, condom distribution, and mobile clinic services, through which we progressively integrated education and awareness of PrEP and early ART. As a core feature of the SWP, interventions were designed around outreach which was identified as a central aspect critical to generating demand and recruiting participants for TAPS. Through this activity, we noted working hours and environmental contexts, created hot spot maps to focus recruitment efforts, and learned about community perspectives of PrEP and early ART.

Feedback collected during outreach in the form of field notes provided contextual information as to where and how sex workers operated and how they interacted with health services, informing viability of given sites. Cursory understanding of the interventions and how they might be taken up and used, determined which supportive structures would be needed and how messages would have to define the differences between PrEP and early ART. These outcomes are described in further sections.

Site assessments and selection

Assessments were conducted in five sites, after eliminating other sites spanning multiple provinces in the Wits RHI SWP. The five sites featured existing SWP clinics already delivering ARVs per national guidelines or sites with plans to implement new clinics, interest and support from the local communities, and potential access to a large group of FSWs in areas where HIV prevalence was high. This information came from the initial consultations and community engagement and mapping, as well as internal programme data. The five sites were: Ngodwana (rural village in Mpumalanga province), Phongolo (rural trucking site in KwaZulu Natal province), Hillbrow (central, inner-city Johannesburg), City Deep (peri-urban trucking site immediately south of Johannesburg), and the Pretoria central business district (CBD), the latter three of which were located in Gauteng province.

Narrowing the site selection was a critical step in moving forward with the design of the interventions. We aimed to select 2-3 sites (according to funding and capacity for oversight) with the following population criteria: access to a large number of FSWs (>200 according to early sample size calculations (17)), populations with a relatively balanced proportion of HIV-negative and HIV-positive women, and accessibility of clinics. Physical feasibility of the clinics to implement the interventions was assessed through reviews of space, clinical and laboratory infrastructure, required site permissions and approvals, and supply chain mechanisms. Support for the interventions was explored with local DoH and sex worker communities, as well as identification of logistical gaps. Site visits, hot spot mapping, and site assessments were conducted to determine the feasibility of delivering PrEP and early ART in each of the five sites.

Hot spot mapping was conducted to determine the number of FSWs working near the potential study sites as well as their working hours. The methods utilized and built on the results produced by the South African Health Monitoring Study (SAHMS), which drew on multiple mapping methods including time-location and the “wisdom-of-crowds” (15). This

activity in combination with prior experience derived through the SWP, revealed that time and location of sex work is driven by client availability. Peak working hours were recorded in each site as critical data dictating when women could be free to attend the clinics. Local languages at each site were also documented so that study materials could be translated and appropriate staff hired.

Following the site assessments, three sites were eliminated. Ngodwana was eliminated due to lack of infrastructure and building delays, as well as lack of local support. Although there was initial interest, the implementation of the interventions potentially conflicted with limited resources and competing priorities in the area. The rural sex worker community in that location do not self-identify as sex workers which would have created challenges in being able to compare formal sex workers who self-identify and those who do not as part of project evaluation. The prevalence of HIV in Ngodwana was estimated locally to be around 75-80% in a relatively small village of <300 people mostly made up of sex workers, which also would have made it difficult to implement PrEP.

City Deep was eliminated due to low clinic attendance, as well as the highly transient nature of the sex worker populations. Most of the women attending that clinic in arrived in the trucks coming from all over South Africa as well as neighbouring countries, which would have made commitment to regular, repeat clinic visits difficult. The Phongolo site, located next to the Swaziland border, was also eliminated as women tended to move in and out of the town and were away for as many as three to four months at a time.

Two sites were finally selected: Hillbrow and Pretoria. Hillbrow was chosen because of the long-standing Wits RHI sex worker clinic which maintains strong ties to a large community of sex workers and their managers (brothel owners, 'pimps'). At the time, HIV prevalence was estimated locally at around 50%. The clinic is situated in an area with a high concentration of brothels and street based locations within walking distance, but also with a number of surrounding outreach areas in the Johannesburg CBD, Yeoville, Jeppe, and Rosettenville. For these reasons, this site was considered "low-hanging fruit" for new intervention implementation, due to the substantial population of women at risk of HIV infection and as a location with solid community support.

In Pretoria, tailored sex worker services and relationships with the community were new at the Sediba Hope clinic in the heart of the CBD, however there was strong support from the local

DoH and expressed need from the sex workers themselves. The newness of such interventions in the area posed a challenge as to whether PrEP and early ART could be implemented within a new sex worker clinic in a new setting, and what it would take to do so.

After final site selection, further identifying and understanding the contexts in which the women worked and lived, as well as their perspectives of those environments, was explored through more intensive outreach and community engagement to determine, on a granular level, how the interventions could fit into their lives. Through the existing, long-term work of the SWP, there was awareness of different types of sex work locales, however the formative research allowed for a deeper understanding of how these locales affected women's lives, and how they might affect their ability to take up and use the interventions.

We assumed three general categories of sex work locales within the two urban settings. Brothels or hotels usually offer alcohol and entertainment, including combinations of music, dancing, and bar games. Many are former or existing hotels while others are simply bars with backrooms. Security protecting sex workers from violent clients is common in these establishments. Secondly, street-based sex work occurs in high traffic areas where sex workers pick up clients, and either join them in vehicles or have sex in a nearby location such as an alley. The third category comprises the "dark places" (IsiZulu: *mnyamandawo*), informal locations in empty lots or other uninhabited/unoccupied buildings or areas where sex workers build rudimentary structures in which to work.

In both cities there is also a fourth, more hidden sex work market found online. Awareness of the online market was generated through conversations with sex workers during outreach and through peer educators, some of whom had online pages and knew of others with similar arrangements. Sex work conducted online usually involves regular clients met through a web-based connection, where business is conducted out of private spaces (personal homes, private spaces run by an owner, upscale hotels or clubs). This population was engaged later in the process as they are less visible to implementers and researchers, and difficult to build relationships with given their desire for anonymity.

The different types of locales dictated how outreach needed to be conducted in order to generate demand for the interventions. In brothels it was possible to hold group health talks in spaces lent by women or brothel managers, but engaging with women on the street or dark places required time to build trust and a certain level of discretion to avoid unwanted

attention. Careful planning around space needs (setting up a rented or borrowed space for sex workers based on the street, or bringing a mobile clinic) was also necessary in these locales. Similarly, it was not possible to go to a place of work to conduct health talks and recruitment for participants identified online, rather relationships were developed with one or two women who could act as advocates for the interventions within their community.

The different risks and benefits for sex workers in each locale type were important to take into account. In brothels, women are protected by managers, staff, and security. On the street and "dark places" there is little or no security, unless organised by a pimp or a gang. Stories of violence and rape were commonly recorded throughout the formative work. Women reported violent interactions with clients, managers, community members, and often the police. These interactions highlighted the need for supportive referral structures, including for mental health, serious injuries, and criminal issues.

Earning ability, directly associated with the type of sex work locale, was identified as an important aspect of being able to take time off to come to the clinic even for short periods of time. Sex workers operating in brothels tend to be able to charge higher rates for sex, usually between R50 and R150 (about 3-10 USD), depending on the status of the brothel and the cost of room rental incurred by the sex workers. On the street, rates are around R50, and in a dark place sex can be R20-30 (about 1.30-2 USD). Making less money meant more difficulty in taking time away from work to attend the clinic for regular PrEP or treatment related appointments.

Development of supportive structures and messaging

During consultations, a number of stakeholders provided views on possible components to be incorporated in the intervention design, in particular supportive structures. Mechanisms for supporting intervention adherence and retention in care were explored, however we decided only to consider those which could also be incorporated into a national programme. Among the possibilities were the use of MEMS caps (electronic bottle caps which would count bottle openings as a proxy for pill withdrawals and thus, adherence), pill counts (as conducted in clinical trials), and mHealth solutions in the form of short message service (SMS) messages. After discussing options with DoH partners, it was concluded that SMS as demonstrated by the ongoing MAMA Connect project (24), could be scaled up in a national programme, whereas other options would not be feasible.

A participatory process led by representatives of RHI's mHealth and Mental Health teams was undertaken through a series of workshops where themes around healthy living were developed followed by relevant SMS messages by peer educators. Both male and female sex worker peer educators worked in groups to create the messages which aimed to encourage healthy choices and wellness. These messages took into account the importance of avoiding inadvertent disclosure of HIV status to non-participants, and could still be used by the SWP after TAPS concluded. This process produced 110 SMS messages which would be sent once a week in succession to all participants who signed up for the service.

Experiences from early outreach activities directly influenced the messaging employed in each location, as well as educational materials used as part of supportive structures for generating demand and promoting awareness of the interventions. Messages focused on defining the interventions, addressing common myths and concerns around side effects, and providing information on efficacy and access.

Peer educator and potential user feedback indicated that personal testimonies are highly valued by women in both locations, so these were included on the informational pamphlets. Trained peer educators also enrolled in the study were invited to become ambassadors for the interventions so that they could directly relate their experiences and dispel rumours about side effects.

Finally, additional supportive structures for the interventions and the women using them included the CAB, as well as tried and tested referral systems where we could ensure women would get additional support beyond the scope of our clinics as needed. One result of the consultations, as well, was the need for holistic sensitivity training around sex work which was conducted with every staff member, from cleaner to clinician, at both sites. Although a more passive support mechanism provided by a local community partner organisation, this was important in ensuring women felt welcome at the clinics.

Focus Group Discussions

FGDs were conducted in the Hillbrow and Pretoria CBD sites following site selection as the final set of activities in the formative research process. The FGDs aimed to test the core intervention design components for acceptability among potential users within the target communities. Four FGDs were held in each site with a total of 69 participants. The FGDs comprised important final steps in informing design as they explored a more focused

community perspective of intervention acceptability on two main levels. One level consisted of data concerning logistics and preferences around physical delivery (location, preferred clinic times, frequency of visits and HIV testing), while the other level included social and structural level data where elements of stigma and socioeconomic norms (e.g. where the need for income might supersede health) that might affect uptake and use of PrEP and early ART were explored. Since this paper is focused on feasibility and early stages of acceptability, the end-stage formative data from the FGDs are presented in a companion paper (25).

3.3.5. Discussion

In this paper, we have described in detail the formative research process and findings used to inform the design of the PrEP and early ART interventions implemented in TAPS. The inductive approach afforded a breadth of information around potential site locations, community and stakeholder perspectives, including potential barriers to successful implementation, and nuanced aspects of the urban sex work settings for considering how to ensure the interventions accomplished reach, accessibility, acceptability, and filled the needs of potential end-users. This process allowed for rapid and relevant consolidation of lessons learned to inform adaptations to the planned interventions.

Feasibility played a significant role in early decision making as to whether PrEP and early ART could be implemented, and acceptability from stakeholders ran in parallel. Questions of feasibility addressed site capacity, experience in delivering ARVs, experience with and access to FSWs, site locations related to FSW populations, and existing supply chains. Early acceptability was determined through consultations and engagement with potential end users in the community during outreach. Factors influencing feasibility and acceptability would not have been as comprehensively understood, such as the day to day clinic operation and the physical contexts and locales of sex work, without repeated site visits and time spent in the field. Continuous, in-depth interactions with the women themselves allowed the TAPS team to better understand sex workers' needs in addition to how interventions reach could be maximized. Additionally, identifying and addressing potential biases from providers and other stakeholders in the provision of the interventions was essential to avoid issues with maintaining permissions and supply chains as well as supportive services.

Generally, it would be expected that sex work populations and industries, with similar urban contexts and in relative geographical proximity, would be the same in both places and that interventions could be implemented uniformly in both locations. However, the formative

research demonstrated just the opposite. While there were some similarities in how women live and work in terms of the types of locales and spaces, there were also significant differences. Sex work locales can be similarly categorised in the two cities, but the organization of these spaces and the make-up of them within Hillbrow and Pretoria is quite different in terms of women's personal safety and earning capability, for example. This translates into different sex worker populations and market dynamics and the need for adaptations to intervention design. Outreach strategies (groups versus one on one discussions) and messaging channels (word of mouth, top down through brothel owners and pimps, or developing online contacts) were dictated directly by context and the expressed needs of the FSWs.

The formative research created awareness for the TAPS team around which stakeholders needed to be involved and engaged throughout the duration of the project, either through the CAB or in regular consultations, as well as the contexts in which women worked and lived and the need to be sensitive around FSW engagement to generate demand for PrEP and early treatment. Without the formative research, we would not have understood the importance of some messages over others from the perspectives of sex workers, the dynamics of sex work locales and their effects on risk and income, nor how flexibility around clinic visit scheduling would need to be taken into account.

3.3.6. Conclusions

The lessons learned from this formative research process were directly applied to the design and implementation of the PrEP and early ART interventions delivered through the TAPS project. The inductive approach afforded the opportunity to adapt and include voices and perspectives, which might have otherwise been missed, and clarified the needs of the population as well as how to reach them appropriately. This research illustrated how sex work environments can vary, even when the settings are very similar, and therefore implementation of interventions is unlikely to be uniform across contexts. Formative research is critical in designing interventions, especially in new environments but also in well-known contexts. Including intensive stakeholder engagement in formative research will help to ensure that interventions are designed with feasibility and relevance for populations in mind.

Declarations

Ethics approval and consent to participate

Formal ethical approval was provided by the Wits Human Ethics Research Committee (reference number: M131009) for the focus group discussions which included information testing and community engagement in the field to inform the development of discussion guides. All documents containing data were saved electronically in central folders with limited access to relevant project staff. No participant identifiers were included in any of the reports that were produced. With regard to other formative research elements, no individual data were collected or reported, and ethical principles of the Helsinki Declaration were strictly adhered to as part of this iterative and flexible approach.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no declarations or conflicts of interest associated with this work.

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Author Contributions

RE developed the research agenda, designed data collection tools, participated in data collection, wrote and collected field notes, analysed the data, and drafted the paper. JM participated in data collection and analysed data. NM and MS participated in data collection. All authors reviewed and contributed to the paper.

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4.0 Chapter 4: FSW community perspectives on the impending implementation of PrEP in their local sex worker clinics

4.1. Introduction

Chapter 4 addresses the research question associated with PhD Objective 3: *What are the community-level perceptions of PrEP in terms of acceptability within the context of imminent implementation among FSWs in South Africa?* Following the practical learning and decision making around intervention design during the formative research presented in Chapter 3, in-depth focus group discussions (FGDs) were undertaken to gain insight into the perspectives of women on the uptake and use of both PrEP and early ART immediately before the launch of implementation through the TAPS Demonstration Project. The paper in this chapter focuses only on the FSW perspectives on PrEP, however, given that it was relatively unknown in this context as compared with early ART. Perspectives of both HIV-negative and HIV-positive women, who were combined in the groups, were included to illustrate some of the overlap in thinking and how inclusive research, implementation and related messaging may better support delivery of new interventions.

Overall, there was significant positivity around PrEP among the women in the groups, and excitement about both PrEP and early ART led them to leave their names on waiting lists to be called when TAPS officially launched. In this way, these groups served as an additional means for early community engagement and education around both interventions where the women who participated in the FGDs could take information back to their friends and colleagues to help spark interest in the interventions.

This work builds on the previous chapter's research which focused heavily on ensuring the applicability of the PrEP intervention was aligned with the needs of FSWs in the chosen sites and contexts. The FGDs then allowed for a narrower focus on the concentrated community perceptions of applicability and acceptability of PrEP (and early ART) as it was to be delivered to them through these local sex worker clinics. These insights helped to situate the impending implementation within the spheres illustrated in the MSEM framework from the community perspective, which is inherently made up of individuals and their experiences, as well as interactions across the social, community, policy, and epidemic domains.

This paper is under review at the Journal of the International AIDS Society, and is one of the first to report FSW perspectives of impending PrEP implementation. It is important to note that these FGDs produced an incredibly rich set of data and at least one further paper is planned to combine FSW views on PrEP and early ART within the context of health service delivery.

The information and consent forms as well as the FGD guide are attached in Appendices vii and viii.

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SECTION A – Student Details

Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

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Please list the paper's authors in the intended authorship order:	Eakle, Robyn; Bourne, Adam; Mbogua, Judie; Mutanha, Nyaradzo; Rees, Helen
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I lead the design of the research, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 5 October 2017

[redacted]

Supervisor Signature: _____ **Date:** 5 October 2017

4.2. Exploring acceptability of oral PrEP prior to implementation among female sex workers in South Africa

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Key words: HIV prevention, biomedical prevention products, pre-exposure prophylaxis (PrEP), sex work, qualitative research

4.2.1. Abstract

Background

Female sex workers (FSWs) are at high-risk for HIV acquisition in South Africa, where the advent of new HIV prevention and treatment interventions represent the potential to significantly impact the epidemic. This paper focuses on aspects of PrEP acceptability as a new intervention within the context of a larger service delivery programme including the simultaneous roll-out of early ART. This paper explores PrEP acceptability among the FGD participants as future potential users.

Methods

FGDs were conducted in two clinic-based sites in Johannesburg and Pretoria. They aimed to explore community-level, multi-dimensional acceptability of PrEP within the context of imminent implementation alongside early ART in the TAPS Demonstration Project. Sex worker peer educators recruited participants from varying sex work locales. Facilitation was in English with adaptation by facilitators into local languages as needed. Transcripts were translated and transcribed into English. Thematic analysis was used to analyse the data.

Results

Four FGDs were conducted in each site for a total of eight FDGs and 69 participants. Demographics were largely similar across the sites. Overall, there was strong acceptability of PrEP among participants and positive anticipation for the imminent delivery of PrEP in the local sex worker clinics. Themes arising from the discussions exploring aspects of PrEP acceptability included: awareness and understanding of PrEP; PrEP motivations including choice, control, and vulnerability, managing PrEP risks and worries; and, de-stigmatising and empowering PrEP delivery. Participant discussions and recommendations highlighted the importance of developing clear education and messaging to accurately convey the concept of PrEP, and intervention integration into supportive and tailored services.

Conclusions

Through the course of these FGDs, PrEP became a positive and highly anticipated prevention option among the FSWs participants who endorsed implementation in their communities. Effective integration of PrEP into existing services will include comprehensive health programming where ART is also available, appropriate messaging, and support.

4.2.2. Introduction

Female sex workers (FSWs) are at high-risk for HIV acquisition in South Africa, with a recent study reporting a prevalence of 72% in the greater Johannesburg area, and 40% and 54% in Cape Town and Durban respectively (1). The advent and success in clinical trials of oral pre-exposure prophylaxis (PrEP) for HIV prevention (2), and test and treat (also 'early ART') for HIV treatment (3,4), represent the potential to significantly impact the epidemic. As a result, these two interventions have become part of the standard of care set out by the World Health Organization (WHO) in 2015 (5).

As countries move towards implementation and scale-up, formative research on the feasibility and acceptability of integrating PrEP and test and treat into local and national programmes is progressing, in particular for target populations (6). However, little has yet been published in low and middle-income country settings about community perspectives on the acceptability these interventions in a context where they are soon to be implemented. The acceptability of, and willingness to engage with, an intervention is central to its development, roll-out and scale-up, and understanding how it is may be perceived by target populations can help counter or mitigate unintended consequences or potential barriers (7,8).

Dimensions of acceptability contributing to successful uptake and use can include personal preferences around ease of use and product attributes; social factors including stigma from partners, family, and friends, and social norms; interactions with medical facilities and service delivery mechanisms; the policy and regulatory landscape; and the context of the HIV epidemic itself (9,10). Some of these elements were explored in previous PrEP and vaginal microbicide efficacy trials, though they more often focused on product attributes (11). Following these qualitative findings, however, a holistic, multi-dimensional approach to acceptability was considered to be critical to promote effective use during scale-up (12).

Given that the transition to PrEP implementation is recent, the multiple dimensions of acceptability are yet to be fully understood as drug-based prevention is unfamiliar to the wider public. Additionally, service providers' experience with rolling out ART programmes, and the delivery of contraception to prevent unwanted pregnancies, could provide a basis for understanding PrEP where services would be similar, but motivations to take the medication would differ in prevention versus treatment.

In this paper, we present findings from focus group discussions (FGDs) that sought to inform the design of oral PrEP and (then called) early ART interventions for FSWs in Johannesburg and Pretoria for implementation in the Treatment And Prevention for Sex workers (TAPS) Demonstration Project. The findings presented here arose in the context of impending PrEP provision, where at the time of data collection, the role and potential of PrEP had not yet been normalised by government guidelines and national regulatory approval. This paper focuses on aspects of PrEP acceptability as a new intervention within the context of a larger service delivery programme including the simultaneous roll-out of early ART. The aim of this paper is to explore PrEP acceptability among the FGD participants as future potential users.

4.2.3. Methods

FGDs were conducted in two clinic-based settings in Johannesburg and Pretoria between July and December 2014. They aimed to explore community-level acceptability of PrEP and early ART interventions with a view to learn how this could influence uptake and use in TAPS. A holistic, multi-dimensional approach to acceptability was employed, including perspectives from both HIV-negative and HIV-positive women on both interventions.

Initial topics for discussion were developed based on the results of an adapted meta-ethnography of women's experiences of uptake and use of biomedical HIV prevention products across sub-Saharan Africa (9,13), as well as the Modified Social Ecological Model (MSEM) designed by Baral et al (14). Discussions encouraged community-level narratives of women's lives and experiences with their work and health services; perceptions of optimal prevention and treatment delivery; knowledge, attitudes, and perceptions of health and well-being, and of PrEP and early ART specifically; acceptability of and commitment to increased, frequent clinical monitoring and HIV testing; and identifying overall motivations and barriers to accessing services, and in particular, PrEP as the newest intervention.

Sex worker peer educators recruited women through their work/social networks from varying sex work locales (brothels, streets, and other informal areas) aiming to gather diverse perspectives from different working and living environments. Discussions were facilitated primarily in English with adaptation by facilitators and staff note takers into local languages as needed. FGDs lasted between one and a half and two hours.

Analysis

Transcripts for each of the FGDs were translated and transcribed into English, then uploaded into NVIVO (version 10.0, Burlington MA). Analysis followed principles of Braun and Clarke's thematic analysis (15) beginning with a set of questions building from themes derived from the discussion guide based on the MSEM but we remained open to new lines of enquiry as they emerged from the data in an inductive manner. The coding framework was devised by the primary author with support from two other researchers, and all transcripts were coded in duplicate by two researchers. Inter-coder reliability was not a focus of the analysis, rather coding choices were discussed throughout and at the end of the coding process to resolve any differences.

Ethical Considerations

All participants provided their informed consent and pseudonyms to protect identities, indicated in this paper as colours. This study was reviewed and approved by the Wits Human Research Ethics Committee (reference number: M131009).

4.2.4. Results

Participant Demographics

Four FGDs were conducted in each site for a total of eight FDGs and 69 participants. Key demographic characteristics are displayed in Table 1.

Table 1. Demographic characteristics of FGD participants.

Characteristics	Hillbrow n=39	Pretoria n=30	Total
Age			
20-29	8	15	23
30-44	26	12	38
45+	5	3	8
Relationship status			
Single	35	24	59
Married or steady partner	1	2	3
Divorced or separated	2	2	4
Widowed	1	2	3
Education			
No School	0	2	2
Primary	3	1	4
Grade 8-12	35	25	60
Higher	1	2	3
Place of Birth*			
Gauteng	7	13	20
Other SA Provinces	22	6	28
Other Countries	10	10	20
Place of Residence (by area)			
Hillbrow	20		20
Greater Johannesburg	19	3	22
Pretoria CBD		15	15
Greater Pretoria		10	10
Brits (Northwest Province)		2	2

Note: Other SA provinces = Free State, Eastern Cape, KwaZulu-Natal, Limpopo, Mpumalanga; Other Countries = Zimbabwe, Mozambique, Lesotho; Greater Johannesburg = Central Business District (CBD), Soweto, Yeoville, Berea, Ekurhuleni; Greater Pretoria = Soshanguve, Mamelodi, Atteridgeville
*1 participant did not list place of birth in Pretoria

Participants were not asked to disclose their HIV status, however most participants did so of their own volition during the discussions. From their disclosures we estimate about 50-75% of the participants were HIV-positive, which is similar to the estimated prevalence in the greater Johannesburg area (1), and to what was observed in Pretoria during outreach and HIV testing during formative work.

While there was relative diversity among the FGD participants, themes arising from the discussions did not differ across the groups. To qualitatively assess overall aspects of PrEP acceptability, we review the thematic findings here in terms of: awareness and understanding of PrEP; PrEP motivations including choice, control, and vulnerability, managing PrEP risks and worries; and, de-stigmatising and empowering PrEP delivery. Quotes from participants are

labelled with their chosen colour pseudonyms, abbreviation of site location (JHB=Johannesburg; PTA= Pretoria), and FGD number.

Awareness and understanding of PrEP

Prior awareness of PrEP was explored within the context of existing or known HIV prevention options. Most of the discussion centred on male and female condoms, however some women acknowledged male circumcision and prevention of mother to child transmission (PMTCT), and some had heard of, or participated in, studies involving the vaginal gel and ring. Aside from condoms, post-exposure prophylaxis (PEP) was most often discussed, along with STI treatments and/or the morning after pill for unwanted pregnancies. *"If you do sleep with a client and a condom gets broken …. everybody decides to drink that pill. But it's just for cleaning, we know it doesn't prevent HIV"* (Brown, PTA 3). Considering PrEP within the context of other previously known options, or lack thereof, allowed women to recognise and interpret PrEP as a potential choice for prevention.

Prior to a detailed description of PrEP within the FGDs, awareness was low. Initial understanding of PrEP was usually reached by equating it with contraception. "*Okay meaning that people who are going to take this tablet they must be very careful because a pill for preventing, it's very risky, because once you forget …. like on birth control pills, it's very risky ….*" (Red, PTA 4). Alternatively, the concept of PrEP was further assimilated through prior knowledge and experience with HIV testing and ART.

Questions relating to awareness and understanding of PrEP frequently resulted in discussions about what type of woman could and should use PrEP, or who would make a "good PrEP taker". There was universal understanding of motivations to take PrEP for HIV-negative women, however it was the need for a certain degree of commitment which the participants focused on:

> "*She has to take care for herself …., so she must behave like a person who prevents when she is avoiding to fall pregnant. But she shouldn't be like when someone prevents and they skip a pill and they would say 'aggh even if I forgot to take my pill nothing will happen to me'. So with PrEP she must continue using it every day"* (Green, PTA 4).

PrEP motivations: choice, control, and vulnerability

An awareness of the high prevalence of HIV among FSWs in their communities underscored the need for more prevention options to safeguard those who were still HIV-negative. *"The*

methods are very limited. …. The only method that we know so far is to use a condom, and.... it can burst anytime" (Brown, JHB 1).

These sentiments laid the groundwork for seemingly universal approval and anticipation of PrEP, which FGD facilitators indicated would be imminently offered in the clinics in their locality:

> *"People are dying outside of HIV. And HIV is spreading so fast …. At least people who are still negative will have a chance to stay negative…. So the spreading of HIV will get limited. Then as time goes by the HIV rate will go down …. I don't want my daughter to go through what I am going through now."* (Brown, JHB 1).

All of the women immediately saw the benefit of having PrEP in the body, especially given that condoms often burst or were removed. *"PrEP is good because it's good because it stays in your blood"* (Red, PTA 3). As sex workers, participants reported how they frequently found themselves in vulnerable positions with clients, which could be hard to anticipate or plan for. In such circumstances, PrEP could be invaluable in protecting women from HIV where they would have personal control over one method of protection. "*Even with a client in your own house, they can throw away the condom, strangle you and leave you helpless because you do not want to use a condom. And do as they please with you"* (Purple, JHB1).

Experiences of sexual violence were frequently reported (unprompted) within groups, and were seen as particularly motivating for PrEP uptake and use. *"Another thing, as a sex worker, there is no one here who say they not been gilwa (treated badly). Maybe they even, some of us we have even been ganged raped. So I believe we have to test continuously, time and again"* (Brown, JHB 1).

Finally, in their own recognition that the primary HIV risk for FSWs came from their main partners rather than clients, many participants reflected on the utility of PrEP in protecting them in the likely event that their partner was also having sex with other women:

> *"Even if she says, that boyfriend, she loves him, there are many hotels. He doesn't have her only. The other hotels there are many he's got another girlfriend, the other hotel, he's got another. And he's been sleeping with them without that condom"* (Red, JHB1).

Such sentiment informed a belief expressed by many that PrEP should be made available to all women, rather than just FSWs. "*Yes I also agree with them that the entire woman should use*

PrEP who are HIV-negative because again they also don't know who their husbands are sleeping with" (Brown, PTA, 4).

Managing PrEP risks and worries

While the potential to reduce HIV transmission was keenly recognised and appreciated, women were also acutely aware of a range of other risks in their sexual, social and personal environments that might influence their willingness to use PrEP. These would, they felt, require careful consideration and management.

A primary concern related to the potential discontinuation of condom use in the context of PrEP, and the implications of this for acquisition of other sexually transmitted infections (STIs) or unwanted pregnancies:

> *"But what I think, neh, if they are going to use these PrEP pills they have to teach people well, that they must use condoms. Make them to be aware of what is going to happen because of, if they say ok you can keep on drinking these pills they will start forgetting to use condoms and start to sleep around without. That's why they're scared, that many teenagers of South Africa, they will have plenty of babies"* (Red, JHB 1).

All of the women agreed that PrEP could not take the place of condoms, and that the two should go together in order to prevent other STIs and unwanted pregnancies, especially since most of the women acknowledged not using other modes of contraception. This perception reflected a general sense that PrEP would serve as useful backup when condoms failed, rather than being seen as the primary prevention strategy.

The risk of potential non-adherence, and thus diminished PrEP effectiveness, was commonly expressed. Many participants felt that some women may not be sufficiently motivated to take a pill every day, especially when they were not feeling unwell. This experience was reflected by some in the group who disclosed their HIV-positive status:

> *"It's difficult to support somebody who's not sick and say she must take medication especially every day. At the clinic they will always check and tell you that your viral load is high, but you will tell yourself that there is no need to take that medication, rather take drugs and you will be ok"* (Brown, PTA 3).

Additional worries around adherence included substance use (alcohol and illicit drugs) and the potential for forgetting to take a daily pill. *"…. those who are using drugs, they won't be able to take PrEP every day because they will forget under the influence of drugs"* (Brown, PTA, 3). However, there was also discussion about how lessons learned in ART adherence among HIV-positive women could help improve adherence among those taking PrEP, such as aligning pill taking with television shows, using phone alarms, and coming up with strategies to keep pills on hand such as in secret bra compartments.

Importantly, the discussion of substance use raised questions about whether PrEP could be taken even when someone knew they would be drinking or using other substances during the course of the day. "*So this PrEP it's not for HIV-positive, so I want to ask something, is there somewhere where it says don't smoke, don't drink ….?"* (Grey, PTA 4). Explaining that using alcohol or other drugs would not diminish the preventive effects of PrEP was met with approval from the participants.

The perception of potential side effects, especially given knowledge of ART side effects from existing drugs on the market, was seen as a likely major barrier to uptake:

> "*Yes, maybe they will come for counselling first before they take the PrEP right, and then they tell them about the side effects and then a person gets scared of it and say, my goodness no, you know what these side effects are going to do to me, 'they will make me sick, they will make me throw up, I will die' you see that kind of thing, or you will be paining"* (Red, JHB 4).

Interestingly, as a result, participants felt it would be important to ensure clear messaging around potential side effects and their duration was central to in the promotion of PrEP.

Perhaps less common were concerns that focused more on logistical and social aspects outside of the women's control, such as the pills being stolen outside clinics:

> *"They know that this one has come to fetch her pills, they steal them from you, you get hurt. They know that they are going to use the pills as drugs. You know that you will be mugged, they hold you up they stab you, what do you do? You are now not killed because of your AIDS but for your pills"* (Purple, JHB 1).

De-stigmatising and empowering PrEP delivery

The need for supportive, non-judgmental services tailored to sex workers was universally stated. *"It is right that such a clinic is there. …. having such a clinic will make people not shy to*

go to the clinic. They can speak freely, because the clinic is ours" (Black, JHB 4). Indeed, positive interactions in the clinic would motivate women to return: *"….when a clinic treats you well, you return to it, but if they don't treat you properly you don't return"* (Red, JHB 2). Including PrEP as part of this type of service delivery environment was considered paramount to successful implementation.

Additionally, having PrEP offered alongside early ART was considered important in destigmatizing interventions. Stress and panic, especially in environments where HIV prevalence was so high, was widespread, therefore many of the women felt that PrEP presented an opportunity to "de-stress". HIV-negative women felt that with PrEP becoming positive wasn't necessarily inevitable, and HIV-positives felt that having additional protection in the community might result in fewer infections.

The need for social support, often initially voiced by women with ART experiences, was identified universally as a valued component of pill-taking and a way to help ensure commitment:

> *"If you get somebody who supports you in what you are doing it's much more easier for you to continue than when they don't have anybody next to you. Like a person like my sister is my biggest supporter. Immediately when I found out I am positive that's the first person I told."* (Purple, JHB 1).

Finally, flexibility in service delivery was underscored as critical for a successful PrEP intervention. This stemmed from not having much time to go to the clinic due to having to work long hours to pay rent, as well as having become habituated to mobile services in the case of the Johannesburg groups:

> *"I don't pay rent. I do business to feed myself. The other's on the streets they are staying in flats …. they need [money] for rent that's why they work the whole night. So we are different in that, you who is staying in a hotel, you don't have time to come to clinic, you are waiting for a mobile clinic to come, you understand?"* (Green, JHB 1).

4.2.5. Discussion

Our findings indicate strong acceptability of PrEP among FSWs in the two communities and positive anticipation for the imminent delivery of PrEP in the local sex worker clinics. FGD participants in turn provided useful insights into how uptake and use could be ensured by this most-at-risk population in South Africa. These centred on developing clear education and

messaging to accurately convey the concept of PrEP, and intervention integration into supportive and tailored services.

Fitting PrEP within existing knowledge of ART and PEP, while equating it with contraception as a prevention modality, was an effective and naturally developed education strategy among participants. Indeed, this has also been true among researchers (16). In addition, experiences with early ART or PEP can translate to PrEP, such as taking medication every day even while feeling well. Discussions in these FGDs suggested that HIV-negative and positive women could represent valuable support systems, a strategy which was successfully used in another study in Zimbabwe (17), and may prove useful for normalizing and implementing the two interventions in scale-up.

There is limited previously published qualitative research regarding PrEP acceptability specifically among FSWs in sub-Saharan Africa. Most microbicide trials targeted women at high risk, which included but did not focus on sex workers (18–22), aside from some of the nonoxynol-9 vaginal gel studies (23,24). One study on intermittent PrEP in Kenya included men who have sex with men (MSM) and FSWs (25), however, only five FSWs were included and results were not disaggregated. Lenses into PrEP acceptability among sex workers have been made available through research with people who use drugs, such as one Canadian study which found that engaging in sex work was in itself a motivation to take up PrEP (26). While limited in scope, findings from these studies, have pointed to values and perspectives around PrEP particular to FSWs' work and roles as women. This also manifested in this study where the key motivation for use was having an additional layer of protection, and personal control, to safeguard against the unpredictable, such as sexual violence at work or lack of condom use with main partners having an unknown status with whom condom use was seen as untrusting or unloving. These dimensions are different than what has been articulated by MSM who have been more concerned with (lack of) accurate risk perception and stigma within their social circles (27), suggesting the need to carefully consider differences in population perspectives when planning to rollout PrEP.

Of particular note were the participants' worries and concerns in our study about the broader effects of PrEP and potential for misuse and misinterpretation. Their recognition, combined with the same awareness among other current and existing users in other parts of the world (27–29), should come as a reassurance to those with apprehensions that the introduction of PrEP could be mismanaged leading to declines in condom use (30).

Finally, data from our study suggest that normalisation may be an important factor when considering PrEP roll-out. There was overall agreement that all women, and even men, should have access to PrEP, and that PrEP should be combined with early ART in the same clinic. The notion of stress around HIV infection was a strong recurring theme, relating to individual disease burden as well as stigma, where a strategy around normalization of both PrEP and early ART could play an important role. The articulation of the stress of HIV and stigmatization of pill taking, points as well to the need to include HIV-positive individuals in the discussion, to garner their perspectives and longer-term commitment to pill taking.

The main limitation in this research is the snowball sampling used to recruit participants which may have resulted in enrolment of more informed or vocal women and/or women who have been continuously involved in sex worker programme outreach activities. However, this was less the case in Pretoria where services had not previously existed. Additionally, the FGDs included only FSWs and took place only in two urban areas, which may limit generalizability to other populations and contexts. The theoretical nature of the FGDs, where actual use was imminent but not yet in place, may not translate into subsequent uptake of PrEP.

4.2.6. Conclusion

Through the course of these FGDs, PrEP became a positive and highly anticipated prevention option among the FSWs participants who endorsed implementation in their communities. Participants shared important insights and interpretations of acceptability for consideration in implementation. Integrating PrEP into existing services as part of a comprehensive health programme where ART is also available, was seen as a best practice, as long as attention is paid to ensuring the appropriate messaging and support are included.

Competing interests

The authors have no declarations or conflicts of interest associated with this work.

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Author Contributions

RE designed the study and data collection tools, participated in data collection, analysed the data, and drafted the paper. AB supported study and data collection tool design and data analysis. JM facilitated data collection and analysis. NM supported data collection. HR oversaw the project as Principal Investigator. All authors contributed to drafting and finalizing the manuscript.

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5.0 Chapter 5: Who used PrEP in the TAPS Demonstration Project?

5.1. Introduction

Chapter 5 addresses the research question associated with PhD Objective 4: *What are key characteristics of FSWs who take up and use PrEP?* This was an important question to address in order to develop a picture of the women taking up PrEP, beyond their personal stories and qualitative perspectives which will be presented in Chapter 6. The aim of examining characteristics was to describe women who wanted, and were clearly motivated, to take up PrEP. These data are relevant both to the applicability and acceptability of PrEP as they illustrate the more profiles of women who took up PrEP when offered, without any other motivation aside from access to PrEP and the clinic.

Each HIV-negative participant enrolled in TAPS, and therefore taking up PrEP, completed an extensive baseline demographic and behaviour questionnaire, however it was not possible to report on every variable in the primary analysis paper upon which this chapter is based. Instead, key characteristics were identified from the literature, including: age, relationship status, country of origin, level of education, and workplace. Several other papers have provided evidence on the importance of these variables in understanding risk profiles of FSWs (1–5). The one variable not as prevalent in this referenced research is the country of origin. This was important to include in the analysis of key characteristics due to the high volumes of women from neighbouring southern African countries who are often even more marginalised than their South African counterparts as targets of xenophobia. These variables illustrate individual characteristics which interact mostly with the social and sexual networks sphere of the MSEM framework.

At the risk of repetition, the results presented in this chapter which are salient to this PhD are highlighted here.

- The majority of FSW participants were between ages 21-30, married, had or lived with a steady partner, completed some or all secondary education, worked in brothels, and were born in Zimbabwe.
- Women consistently reported high condom use with clients and low condom use with main partners.
- Women had higher rates of STIs at baseline than during the rest of the study.

Interestingly, the descriptive analysis of these variables combined with the analysis of behavioural characteristics, including condom use with different partners and STI rates, suggest that FSWs who were at a self-recognised high risk of HIV infection took up PrEP. These findings, combined with the perspectives on PrEP use collected from a selection of the women in the study presented in Chapter 6, make for a compelling story of self-selection and risk perception which may be, key in driving interest in PrEP.

A more in-depth regression analysis is planned using the larger demographic and behaviour data set and linked to the self-reported adherence data as well as the results of PrEP drug level analyses which are currently pending. This analysis will aim to look at correlates of PrEP use over time, as well as correlates of uptake as compared to those who screened but did not enrol in TAPS. Depending on the availability and comparability of the data sets, we may also conduct comparative analyses with Wits RHI's larger Sex Worker Programme clinic data. There is also a mathematical modelling activity underway which will examine in more detail the potential impact and cost-effectiveness of PrEP in this population. These additional components, however, are beyond the scope of this PhD.

The information and consent forms for the main TAPS research which are included in Appendix ix. The baseline demographic and behaviour survey for TAPS from which the key characteristics were derived is attached in Appendix x. STI data were aggregated from the clinical records. Note that supplemental material was only included as it relates to this PhD and will be included after the paper references.

This paper has been submitted to PLoS Medicine and is pending editorial review of final revisions.

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SECTION A – Student Details

Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS Med
Please list the paper's authors in the intended authorship order:	Robyn Eakle, Nyaradzo Mutanha, Judie Mbogua, Maria Sibanyoni, Adam Bourne, Gabriela Gomez, Francois Venter, Helen Rees
Stage of publication	Undergoing revision

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I partnered with Dr Gabriela Gomez, Prof Francois Venter, and Prof Helen Rees on the design of the research. I am Co-Principal Investigator on the study and project lead. I led the development of most of the data collection tools. Dr. Gomez led the statistical

	analysis with support from me. I conducted all of the qualitative analysis. I lead the drafting of the manuscript.

Student Signature:  **Date:** 5 October 2017

Supervisor Signature: _____ **Date:** 5 October 2017

5.3. Pre-exposure prophylaxis and early antiretroviral treatment for HIV prevention and treatment among female sex workers in South Africa: results from a prospective observational demonstration project

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5.3.1. Abstract

Background

Operational research is required to design delivery of pre-exposure prophylaxis (PrEP) and early antiretroviral treatment (early ART). This paper presents the primary analysis of programmatic data, as well as demographic, behavioral, and clinical data from the TAPS Demonstration Project which offered both interventions to female sex workers (FSWs) in two urban clinic sites in South Africa.

Methods and Findings

The TAPS study was conducted between March 2015 and June 2017, with the enrolment period ending in July 2016. TAPS was a prospective, observational cohort study with two arms delivered in existing service settings: 1) PrEP as part of combination prevention for HIV-negative FSWs, and 2) early ART for HIV-positive FSWs. The main outcome was programme retention at 12 months of follow up. Of the 947 FSWs initially seen in clinic, 692 were HIV tested. HIV prevalence was 49%. Among those returning to clinic after HIV testing and clinical screening, 93% were confirmed clinically eligible for PrEP (n=224/241), and 41% (n=110/270) had CD4 counts within NDoH initiation guidelines at assessment. 93% of those remaining were eligible for early ART (n=148/160). From those eligible, 98% (n=219/224) and 94% (n=139/148) took up PrEP and early ART, respectively. At baseline, the majority of women were married or had a stead partner, worked in brothels, and were born in Zimbabwe. Of those enrolled, 22% on PrEP (n=49/219) and 60% on early ART (n=83/139) were seen at 12 months, while we observed high rates of loss to follow up 71% (n=156/219) and 30% (n=42/139) in the PrEP and early ART arm, respectively. Little change over time was reported in consistent condom use or the number of sexual partners in the last seven days, with high levels of consistent condom use with clients and low use with main partners in both study arms. There were no seroconversions on PrEP and seven virological failures on early ART among women remaining in the study. Reported adherence to PrEP varied from 70 to 85%, whereas over 90% of participants reported taking pills daily while on early ART. Provider-side costs were also collected and analysed. The total cost of service delivery was approximately $126 for PrEP and $406 for early ART per person-year. The main limitations include lack of comparison arm not included due to ethical considerations, clinical trial requirements imposed when PrEP was not approved through the regulatory system which could have affected uptake, and the timing of implementation of the national sex worker programme which could have also affected uptake and retention.

Conclusion

PrEP and early ART services can be implemented within FSWs routine services in high prevalence, urban settings. We observed good uptake for both PrEP and early ART, however retention rates for PrEP were low. Retention rates were standard for early ART compared to current standard of care. While the cost of the interventions is higher than previously published, there is potential for cost reduction at scale. The TAPS demonstration project results provided the basis for the first government PrEP and early ART guidelines and the roll out of a national sex worker plan in South Africa.

Author summary

Background

- Nearly two million people still become infected with HIV every year, mostly through sexual transmission. These infections occur more often in vulnerable populations where people do not always have the access or option to use HIV prevention.
- Antiretroviral-based drugs, normally used to treat HIV, have also been shown to prevent transmission both by giving the drugs to HIV-negative people to prevent them from getting HIV (called pre-exposure prophylaxis or PrEP) and treating HIV-positive people earlier (called early ART).
- These interventions are now being piloted by national programmes to test whether (and how) they can be successfully delivered in clinics and the public sector.

Why was this study done?

- Female sex workers are a vulnerable population at risk of HIV, and in some areas of South Africa, nearly three out of four sex workers are already infected.
- We conducted a study located in existing, sex worker-specific clinics to see if female sex workers would take up and use PrEP and early ART if these interventions were offered.
- This was one of the first studies of its kind to be conducted in Africa. We partnered with the South African government so that they could see how the interventions worked and what it cost, to incorporate them into national HIV programming.

What did we do and find?

- We offered PrEP to HIV-negative and early ART to HIV-positive female sex workers in two clinics located in Johannesburg and Pretoria in South Africa. Over time, we

assessed how many women were contacted for the intervention within communities, how many came to the clinic for HIV testing, how many were HIV-negative and positive, and how many took up the interventions. We then monitored those who participated for at least 12 months to see whether they stayed in the programme and used PrEP or early ART.

- The primary goal was to see how long women stayed in the project. We also looked at how well they took their medications, any safety or other clinical issues, and collected data on their demographic and behaviour characteristics.
- We found a HIV prevalence of 49% among 692 women tested. Among those returning to clinic after HIV testing and clinical screening, 93% were confirmed eligible for PrEP, and 94% for early ART. From those eligible, 98% and 94% took up PrEP and early ART, respectively.
- These women were mostly married or had a steady partner, worked in brothels rather than on streets, and came from neighbouring Zimbabwe.
- At the end of the 12 month assessment, 22% remained on PrEP, while 60% remained on early ART at our clinic sites. It is possible that some women moved to other sites without our knowledge, as other sites started offering PrEP and early ART. The drugs were safe to use with few side effects. We also found that women who stayed in the study reported taking their pills regularly. None of the women who remained in the study in the PrEP arm got HIV, and very few women taking early ART had issues supressing the virus. The overall cost of the programme came to approximately $126 for PrEP and $406 for early ART per person-year.

What do these findings mean?

- These findings suggest that female sex workers may be interested in both PrEP and early ART and that the interventions work well when taken, but longer-term commitment may be a challenge.
- These interventions have already been introduced by the South African government into sex worker programmes, including male, female, and transgender people.

5.3.2. Introduction

Rates of new HIV infections remain high, especially in key populations in sub-Saharan Africa, necessitating new options for HIV prevention and treatment [1,2]. Mathematical and clinical studies suggest that a programme combining current HIV prevention options with oral pre-exposure prophylaxis (PrEP), i.e. giving antiretrovirals (ARVs) to an uninfected individual, and early antiretroviral treatment (early ART), i.e. giving ARVs to an HIV-infected person irrespective of CD4 count, could make significant inroads on reducing new infections in key and general populations [3–7].

Following the transition of WHO treatment guidelines to recommend both PrEP and early ART, research has shifted focus to answering questions about implementation [5] including uptake, adherence and retention in existing programmes [8]. Demonstration projects, open-label extension studies and population-based implementation trials testing feasibility in 'real-world' settings, are ongoing or have been recently completed [9,10]. Most of the completed demonstration projects have focused on men who have sex with men (MSM) populations throughout the world (though primarily in the United States, South America, and Europe) [10]. One or two other projects have been completed among serodiscordant couples [11], and only one randomized control trial implementation study had been completed among female sex workers (FSWs) at the time of writing [12].

In South Africa, although sex work is still criminalised, female sex workers (FSWs) have been prioritised for focused, tailored services in the previous and new National Department of Health (NDoH) National Strategic Plans (NSPs), as well as a specialized plan for sex workers, as a population with the highest incidence and prevalence of HIV, especially in urban areas [13–15]. This included support for demonstration projects to further the development of specialized services including PrEP and early ART.

The TAPS Demonstration Project (Treatment And Prevention for female Sex workers), nested within the long-standing Sex Worker Programme [16], was designed to support integration of oral PrEP as part of a combination prevention approach and early ART in two urban settings with specific aims to assess uptake, retention, and adherence among FSWs and to estimate the cost of this strategy. TAPS was the first demonstration project in South Africa to include PrEP and early ART for FSWs, and among the first few in sub-Saharan Africa as well. This paper presents the primary results.

5.3.3. Methods

The TAPS Demonstration Project was a prospective, observational cohort designed as a 'real-world' implementation study to integrate PrEP as part of a combination prevention approach and early ART into existing services for evaluation. The protocol has been described in detail in a previous publication [17].

Setting and intervention

TAPS was embedded within the Sex Worker Programme (SWP), operated by Wits Reproductive Health and HIV Institute (Wits RHI), which is integrated into the South African public health clinical service. The SWP has been in existence since 1996 and is run by nurses, community health workers, and peer educators [16]. Systematic formative research conducted to support the design and in preparation for TAPS is presented elsewhere [18].

The two clinic sites were situated in inner-city Johannesburg and Pretoria. These clinics cater to an urban population of sex workers working in hotel brothels, on streets and in other informal environments. The clinics provide standard of care primary healthcare including HIV testing services (HTS), male and female condoms distribution, nurse-initiated and managed ART, tuberculosis screening, contraceptive provision, cervical cancer screening, clinical services for STIs and minor ailments, psychosocial support, and referrals for pregnancy and other clinical and legal services.

Recruitment of FSWs took place in the clinics and in surrounding brothels, bars, and streets, relying on existing peer educator outreach services. Screening for participation was conducted in two steps. First, women were tested for HIV using a standard of care rapid test. This step included obtaining NDoH HTS written consent and asking brief questions as to current pregnancy and whether they were a sex worker (e.g. they were asked to self-identify after peer recruitment in their places of work). Women were then either referred to other relevant care (if they were pregnant, not a sex worker, or decided not to proceed), or they continued onto clinical screening for the TAPS study. This process always occurred on the same day to ensure that HIV testing and clinical assessments were aligned. The next phase of the screening process began by obtaining study-specific written consent, then continued with the assessment of clinical history, administration of demographic and behavioural questionnaires, tuberculosis (TB) and pregnancy screening, blood draws for creatinine, hepatitis B screening, and syphilis testing. HIV status confirmation with ELISA was done for HIV-positive participants at a private laboratory where all the other samples were also analysed. Women were offered

contraception, as well as the need to use condoms to prevent HIV, STIs and unwanted pregnancies.

After screening, participants were asked to return a week later, to allow for laboratory analyses to be completed, for potential enrolment into either PrEP for HIV-negative FSWs or early ART for HIV-positive FSWs. The definition of the latter has evolved in line with national guidelines. At the start of the study the CD4 threshold for treatment initiation was 350 cells/mL, this changed to 500 cells/mL, and then independent of CD4 count during the course of the study. Since our purpose was to offer treatment to those outside of the guidelines, TAPS transitioned with the national treatment initiation definition. Project milestones are provided in supplementary material (Supplementary material, Figure S1). Women were eligible for the study if they were: age 18 or over, not pregnant at enrolment, did not have multi-drug resistant TB, not participating in another clinical study, and had finished their regimen for post-exposure prophylaxis if they were taking it at the time of assessment. Those who became pregnant through the course of the study were given the option to remain in the study on current medication, discontinue use during the period of pregnancy and remain in the study, or transfer out completely to antenatal care (ANC). The first two options also included referrals to ANC.

Once initiated on PrEP or early ART, participants were scheduled for an initial one-month check-in to assess safety and/or adherence issues, and then scheduled for quarterly clinical testing and safety monitoring visits thereafter. All clinical monitoring followed South African national guidelines throughout the study (also detailed in the published protocol) [17] and all services were provided free of charge as per the public health clinic standard, including PrEP and early ART. Participants were given refills of 1-3 months depending on ability to safely store the products and desire to come to the clinic for refills. The importance of consistent and high adherence was emphasized during PrEP use, however participants could cycle on and off medication during periods of lower risk as desired and remain in the study. Indeed, the PrEP intervention for HIV-negative women included not only the use of PrEP but also other available prevention options (such as condoms, continuous testing and counselling and STI screening). Participants were offered short message system (SMS) reminders around clinic visits and positive messaging around adherence, health and psychosocial issues.

For both arms, participants were asked about pill taking habits with a motivational technique employed at each staff touch point: counseling, clinical, and pharmacy. Counselling followed

the current standard of care for ART provision. Blood samples were taken for analysis of drug levels in the PrEP participant, results of which will be presented at a later date as not currently available. Adverse events were recorded per Good Clinical Practice (GCP) guidelines and WHO recommended grading [19,20].

Evaluation

Programmatic data to describe eligibility and uptake was collected in activity reports including: number of outreach contacts and appointments booked. Routinely collected demographic, behavioural, and clinical data were also analysed. Retention in care at 12 months was the primary outcome. Participants exited the analysis if they withdrew from the study or were lost to follow-up, defined as no contact over two consecutive quarterly clinic visits. Participants were considered retained in the programme if they had not withdrawn or been lost to follow up during this period. We used an adapted cascade approach to measure uptake and retention through a series of "touch points" with participants. These points started during outreach through the enrolment process. Retention data is reported at each of the time points (3, 6, 9 and 12 months). Women who missed visits and returned later were included in the analysis. Data for those women who completed more than 12 months of follow up have been included as part of the supplementary analysis.

Data were analysed on self-reported adherence and sexual behaviour, sexually transmitted infections (STIs), and side effects. We also monitored any possible seroconversions on PrEP and virological failures on early ART. Qualitative research including in-depth interviews (with a selection of up to 10% of study participants), clinic observations, and group discussions with providers was also conducted and will be presented separately.

Costs were estimated from a healthcare provider perspective for each clinic using an ingredient approach. We included capital costs (equipment, buildings, non-recurrent training), as well as recurrent costs (personnel, supplies, management, and maintenance of buildings). Capital costs were annualised. Data collection activities included measurement of clinics, weekly timesheets completed by staff involved in the programme detailing time per programme activity as opposed to research activities, observations of practice detailing all clinical activities during each participant visit, interviews with staff exploring time shared with other programmes as well as review of expenditure and utilization data with regards to the programme. Sources used in the valuation of all resources and methods for allocation of shared resources are detailed in the supplementary material (Supplementary material, Table

S1). We used both bottom-up and top-down approaches to calculate unit cost per visit. Economic costs were assigned to drugs as per procurement prices from NDoH for generics (USD 4.8/month of PrEP; USD 8.3/month of early ART); quantities of drugs dispensed per patient were sourced from clinical and pharmacy records. Services, activities and healthcare providers involved in each type of visit are listed in the supplementary material (Supplementary material, Table S2). We present unit costs for the different types of visits (outreach contact, testing session, enrolment, follow up and refill visits. Our unit costs per person-year for PrEP and early ART include enrolment, follow up and refill visits taking place during the first year of services and reflect the attendance patterns observed during the TAPS Demonstration project. All prices were collected in local currency and are reported in USD 2015. The average exchange rate used was USD 1 = ZAR 11.6. All data were analysed in STATA 12 (StataCorp, USA) and EXCEL 2016 (Microsoft, USA).

A national programme including PrEP and early ART for FSWs was launched in June 2016, during the study, and may have influenced enrollment and retention. To test this, a stratified analysis of uptake and retention indicators is provided in supplementary material by comparing the cascade results along TAPS cohorts disaggregated by time of enrolment and follow up periods. We tested the null hypothesis that the two proportions are the same at each step of the cascade and report p values for this testing. This analysis was the only additional analysis not prospectively defined.

Ethics approval

The TAPS Demonstration Project protocol was approved by the University of Witwatersrand Human Research Ethics Committee (reference number: 140502), the South African Medicines Control Council (reference number: 20140740). All participants completed a written informed consent process for the study consisting of a comprehensive consent form for the main study, as well as additional forms for laboratory sample storage and the qualitative study components. Costing studies were also performed after securing consent from clinic staff.

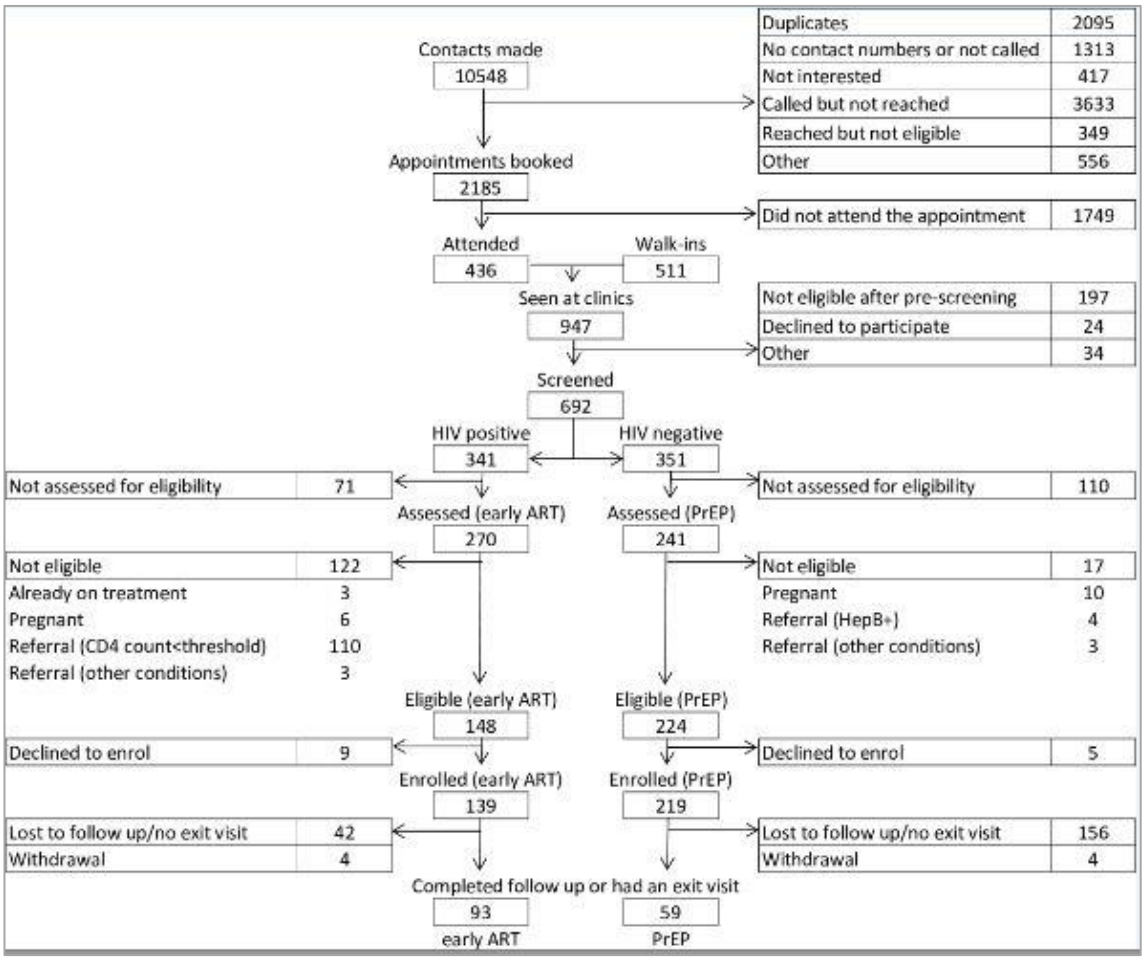
5.3.4. Results

Outreach and uptake

Enrolment for the TAPS study occurred between 31 May 2015 and 31 July 2016. At the end of this period, 219 HIV-negative and 139 HIV-positive FSWs were enrolled.

This process began with outreach and recruitment, where 7,140 FSWs were contacted of the 10,548 names gathered across the two sites, after excluding duplicates and inaccurate phone numbers (Figure 1). This included women recorded on waiting lists leading up to the launch of the study which were compiled during pre-study outreach and community education activities. After making contact, a total of 947 FSWs were seen in the clinic, of which 692 were HIV tested (73%) as per standard of care. At this point, 21% (n=197) of the women were found to be already taking ART, pregnant, or not considered themselves to be sex workers, making them ineligible for enrolment. These women were referred to relevant care options, and therefore did not complete the next phase of study screening which occurred in the same visit as the HIV testing. Among those tested for HIV, there was a prevalence of 49% (n=341/692). Following HIV testing, 79% (n=241/351) and 69% (n=270/341) participants returned for enrolment for PrEP and early ART, respectively. Among the HIV-negative participants who returned for eligibility assessment, 93% were assessed as clinically eligible (n=224/241). Among HIV-positive participants who returned for eligibility assessment, 41% (n=110/270) had CD4 counts within NDoH initiation guidelines at assessment, and 93% of those remaining were eligible for early ART (n=148/160). Reasons for non-eligibility are presented in Figure 1. Uptake among those eligible was high, 98% (n=219/224) of FSWs offered PrEP accepted and 94% (n=139/148) accepted early ART. The detailed numbers of participants at each step of enrolment and follow up are presented in supplementary material (Supplementary material, Table S3).

Figure 1. Flowchart of participant enrolment and follow up



Abbreviations: HepB+, positive result for hepatitis B; CD4 count<threshold, indicates a CD4 count results below the threshold for ART initiation at the time of assessment.

The comparison of TAPS cohorts, both PrEP and early ART, disaggregated by time of enrolment (e.g. before or after the launch of the national pilot), revealed no statistically significant differences throughout the enrolment and retention cascade, aside from two points: number of appointments booked (20% of contacts made resulted in an appointment being booked in the cohort enrolled before the national pilot as opposed to 26% among those enrolled after the pilot) and number eligible for early ART (more HIV positive participants were eligible for early ART in the cohort recruited after the pilot, 95%, compared to the cohort enrolled before the pilot, 51%). In particular, the higher proportion of appointments booked from contacts made among those enrolled post launch of the pilot cohort compared to those enrolled before the pilot could be related to larger recruitment and education efforts at the sites. The higher proportion of participants eligible for early ART in the cohort recruited after the pilot started could be an indication of earlier presentation. The comparison of TAPS cohorts, both PrEP and early ART, disaggregated by completion of follow up period (e.g. 12-month follow up completed before or after the launch of the national pilot), revealed no statistically significant

differences throughout the enrolment and retention cascade. These results are presented in Table S4 in the supplementary material. Further details regarding enrolment statistics over time can be found in the supplementary material (Supplementary material, Figure S2).

Baseline characteristics

In Table 1, selected baseline characteristics of enrolled participants are presented. Women enrolled in the PrEP arm were significantly younger than those enrolled in the early ART arm. Both arms presented a majority of FSWs either married or living with a steady partner (50% on early ART and 56% on PrEP), born in Zimbabwe (48% on early ART, 67% on PrEP), and with secondary education (86% on early ART, and 87% on PrEP). A substantial majority of the participants work in brothels, with 62% in the early ART arm, and 77% in the PrEP arm.

Table 1: Baseline characteristics of FSW participants enrolled (total n=358)

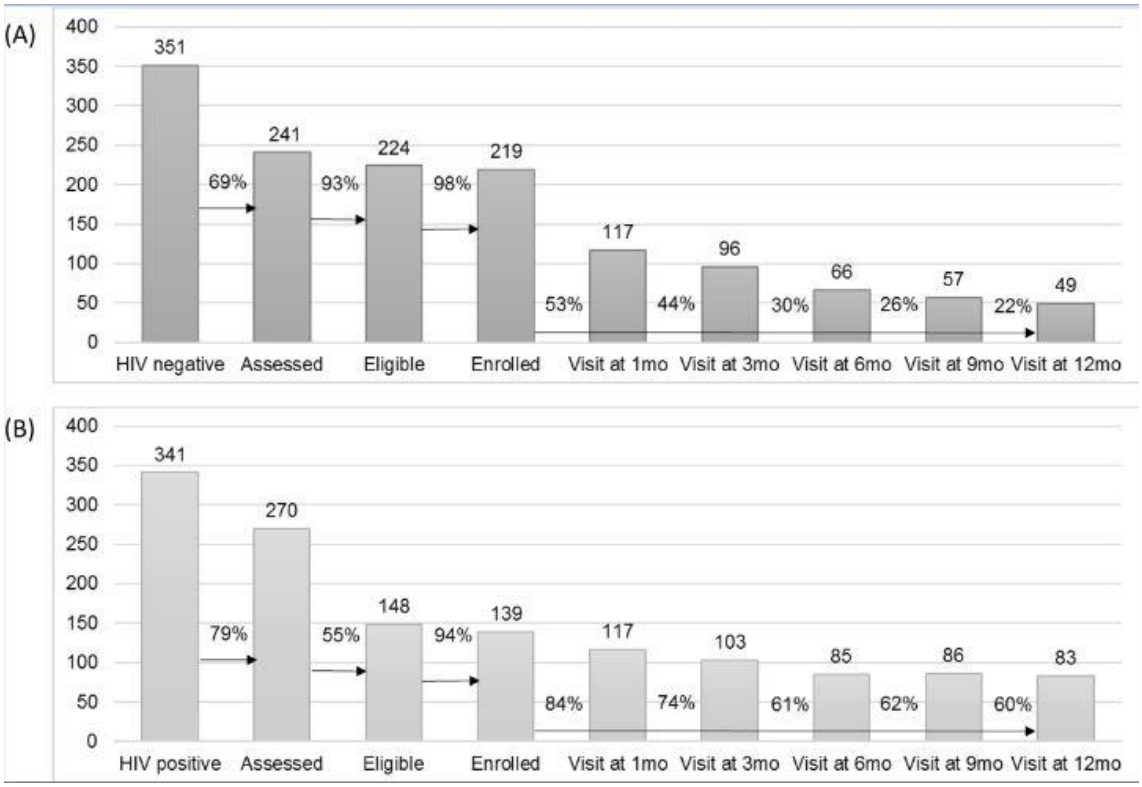
Characteristic	Detail	Early ART (n=139)		PrEP (n=219)		P value*
Age	n, mean (SD)	139	31.9 (6.4)	219	29.8 (5.9)	0.0016
	median (min-max)		31.7 (19.6-40.0)		28.9 (18.0-55.4)	
	18-20 years	1	0.7%	2	0.9%	0.001
	21-30 years	53	38.1%	127	58.0%	
	31-40 years	71	51.1%	77	35.2%	
	41-50 years	14	10.1	10	4.6%	
	51-60 years	0	-	3	1.4%	
Current partnership	No current partner	70	50.4%	102	46.6%	0.599
	Single, no partners at present	64	46.7%	88	40.4%	
	Divorced or separated	5	3.6%	7	3.2%	
	Married and living apart	1	0.7%	7	3.2%	
	Currently in a partnership	67	48.2%	116	53.0%	
	Steady partner, not married/not living together	52	38.0%	85	39.0%	
	Not married but living together	14	10.2%	24	11.0%	
	Married and living together	1	0.7%	7	3.2%	
	Did not answer	2	-	1	-	
Country of origin	Zimbabwe	67	48.2%	146	66.7%	0.009
	South Africa	60	43.2%	60	27.4%	
	Lesotho	7	5.0%	10	4.6%	
	Swaziland	3	2.2%	1	0.5%	
	Mozambique	2	1.4%	2	0.9%	
Education	No education	0	0.0%	1	0.5%	0.107
	Primary	15	10.8%	12	5.5%	
	Secondary	120	86.3%	189	87.1%	
	Tertiary	4	2.9%	15	6.9%	
	Did not answer/does not know	0	-	2	-	
Place of work	Hotel/brothel	86	61.9%	168	76.7%	0.008
	Street	37	26.6%	28	12.8%	
	Home	4	2.9%	5	2.3%	
	Other	12	8.6%	18	8.2%	

Abbreviations: n, number; SD, standard deviation; min, minimum; max, maximum. *All p-values are two sided; differences in means were assessed using t-tests and categorical variables were assessed using chi square.

Visit attendance and retention

During the first 12 months of follow up, 156 and 42 participants (71% and 30%) were lost to follow-up (missing two clinical monitoring visits) or did not complete an exit interview at study closure from the PrEP and early ART arms, respectively. The prevention and care cascades are shown in Figure 2.

Figure 2. HIV prevention and care cascades



(A) HIV prevention cascade: PrEP cohort. (B) HIV treatment cascade: early ART cohort.
Abbreviations: mo, month.

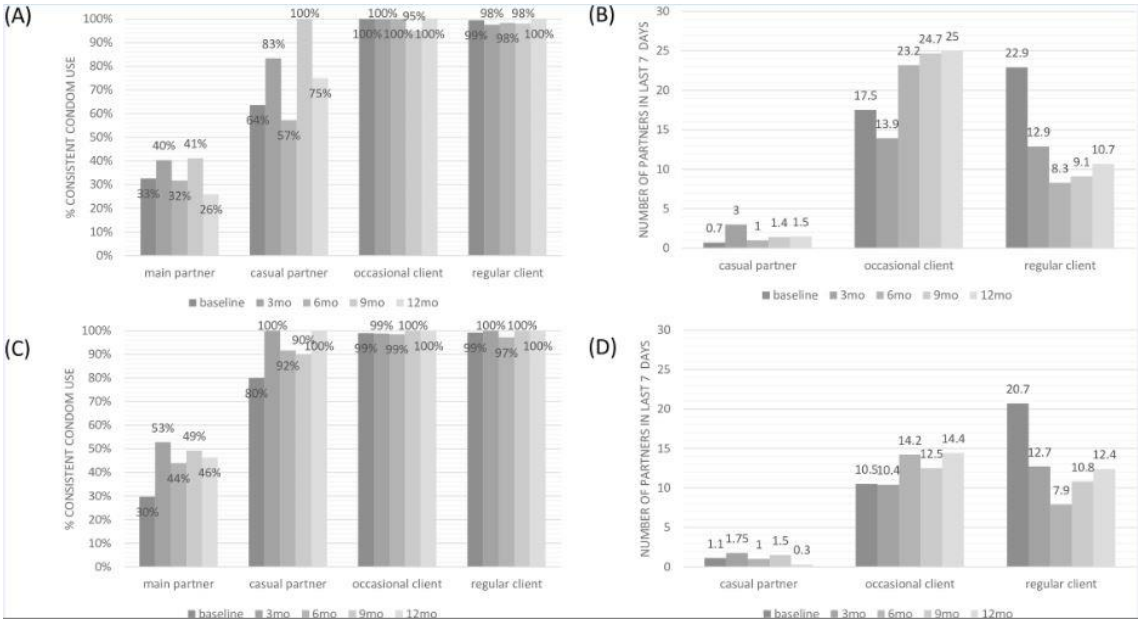
The study follow-up period closed in June 2017. There were 22% and 60% of the enrolled PrEP and early ART cohorts attending the 12 months visit. Overall, programme adherence was higher in the early ART arm compared to the PrEP arm, where participants tended to be less regular in their attendance. This is illustrated graphically in Figure S3 of the supplementary material. Eight women withdrew, four from each arm. Reasons for withdrawal were either side effects or moving to another location. Extended cascade results for those women who attended the study for a period of time longer than 12 months are presented in the

supplementary material (Supplementary material, Table S5). When examining loss to follow up over time, as shown in Figure S4, we observed that most women drop off earlier in the schedule, in particular in the PrEP arm. Denominators for each point in the cascade are also shown in this table and should be taken into account with the loss to follow up over time shown in Figure S4.

Secondary outcomes

In Figure 3, self-reported consistent condom use by partner type and study arm is shown over time. Higher condom use was reported with clients than with partners, especially main partners. Women on early ART tended to use condoms slightly more with casual and main partners, than those on PrEP. Little change in reported condom use over time by type of partner was observed. Additionally, there was no increase in number of partners over time. Further details on these data are presented in Table S6 (Supplementary material, Table S6). Number of STI episodes at baseline and every three months are presented in Table S7 of supplementary material. FSWs had significantly less STI episodes while participating in the study on both arms. These data are presented with the caveat that drop out over time may contribute to bias in the numbers at later time points.

Figure 3. Sexual behaviour over time by partner type: consistent condom use and number of partners in last seven days.



(A) Consistent condom use: PrEP cohort. (B) Number of partners in the last seven days: PrEP cohort. (C) Consistent condom use: Early ART cohort. (D) Number of partners in the last seven days: Early ART cohort.

Abbreviations: mo, month

The proportion of women reporting taking PrEP pills daily varied from 70 to 85%, whereas over 90% of participants reported taking pills daily while on early ART during the first 12 months follow up (Supplementary material, Table S7).

During the first 12 months of follow up, there were seven pregnancies in the PrEP arm. Although women were given the option to continue on PrEP while pregnant, three chose to terminate and continue on PrEP, two were lost to follow up, and only one chose to continue on PrEP in the study while pregnant. There were eight pregnancies in the early ART arm, and an additional four in the extended follow up period, two of which were found at study exit. Early ART participants chose to continue with the study and their pregnancies.

One participant from the PrEP arm who had previously decided to leave the study returned when she had become HIV-positive and was referred for ART initiation. In the early ART arm, there were 12 confirmed cases of virological failure, 11 of which resulted in high level virological resistance to at least one drug (11 with resistance to efavirenz, five to emtricitabine, and two to TDF), among the women retained in the study. One patient had fully susceptible virus at resistance testing.

Of all 692 women who completed the screening process, only one participant presented with serious complicating health issues, including suspected tuberculosis and a creatinine clearance of 50 mL/min. There were no other cases outside the creatinine clearance for initiation of TDF.

PrEP and treatment drugs were well tolerated, with the majority of adverse events being reported as mild for both arms, and few moderate. Of the 306 total adverse events recorded, only 17 were assessed to be drug related: eight on PrEP reported mild headaches, nausea, drowsiness, dizziness, or diarrhea; and nine on early ART reported mild nausea, diarrhea, dizziness, or drowsiness. One participant developed abnormal liver function tests, presenting ill after taking early ART for four months. Liver function tests revealed severely deranged liver function tests, and she was referred to a specialist, where the diagnosis was HIV-induced sclerosing cholangitis.

Finally, in Table 2, both unit costs per visit type and overall cost of a person-year on early ART and PrEP are shown. We found lower unit costs for the visit types involving either low overheads, drugs or tests (i.e. outreach visits) or staff time (i.e. refill visits). The distribution of costs by input is presented in supplementary material (Figure S5).

Table 2. Unit costs per visit and per person-year for PrEP and early ART among FSWs (USD 2015)

Unit cost	Site		
	Hillbrow	Pretoria	Mean
Outreach contact	3.0	2.6	2.8
VCT session	21.2	15.1	18.1
PrEP enrolment visit	40.4	29.0	34.7
PrEP monitoring visit	37.4	33.0	35.2
PrEP refill visit	7.4	6.2	6.8
PrEP (per person-year, y1)	**146.6**	**106.6**	**126.6**
early ART enrolment visit	67.1	64.0	65.5
early ART monitoring visit	72.5	62.9	67.7
early ART refill visit	13.4	9.8	11.6
early ART (per person-year, y1)	**380.5**	**432.3**	**406.4**

Abbreviations: VCT, voluntary counselling and testing, y1, initial year of services.

5.3.5. Discussion

In this prospective, observational demonstration project, we observed high uptake of the PrEP and early ART interventions among eligible FSWs. Retention in the early ART arm was consistent with the national programme [21], while retention in the PrEP arm was lower at the 12-month assessment. There were also few virological failures in the early ART arm and no seroconversions in the PrEP arm. However, given the low rate of retention at the end of the study in the PrEP arm, it is possible that women who dropped out and were not tracked became HIV-positive. To our knowledge, this is the first demonstration project to present results following the integration of a combined PrEP/early ART intervention into an existing sex worker health programme. The results of this project supported the establishment of the first official combined guidelines for oral PrEP and early ART in Africa, as well as the first specialized national programming including these interventions for sex workers in Africa [22,23]. The South African PrEP and early ART (or test and treat) guidelines were launched initially for sex workers in June 2016, where PrEP and initiation of ART irrespective of CD4 count became standard of care for sex workers. Test and treat was then extended to all HIV-positive people in South Africa in September 2016.

Additionally, TAPS has produced two important programmatic findings. Firstly, the high number of women informed about the study translated into a much smaller number actually presenting to take up the interventions. Since both PrEP and early ART are novel interventions, it is possible that as knowledge and use spreads in this community overall uptake might increase, as seen in the introduction of contraception [24]. Normalisation of new interventions

may be key to their successful implementation [25], and this will be explored further in the analysis of qualitative data. Secondly, among those who presented at the clinic, there were high levels of intervention uptake for both PrEP and early ART.

Higher levels of retention were maintained in the early ART, than for the PrEP arm. It is important to note that retention in care refers to two constructs depending on whether participants are being retained in a prevention or treatment intervention. For the PrEP arm, we tried to present results on the continuous contact with healthcare services and access to prevention packages, even though the women were allowed to cycle in and out of PrEP medication use. For the early ART arm, we valued retention in care as an essential component of a successful treatment programme. Interestingly, women who enrolled on PrEP earlier in the study tended to be the ones who continued the longest, suggesting those most motivated, interested, and/or able to take up the interventions came earlier. It is important to note that participants were not reimbursed for their participation, suggesting dedicated sex worker services can result in high levels of engagement in care among FSWs.

We observed a significant participant drop-off between screening and assessment for eligibility. Much of the loss may be directly related to the waiting period between screening and enrolment required for research purposes and to assess laboratory results. This may not reflect service delivery in future programmes where same-day initiation for both PrEP and early ART are being considered. We had only a single creatinine case at screening meriting concern, and immediate initiation with follow up and potential discontinuation for those with concerning results may be possible.

Women who became pregnant in either arm of the study were given options regarding maintaining PrEP use, staying in the study, or transferring into other care. However, only one woman decided to stay on PrEP and continue in the study while three chose to terminate their pregnancies. It is possible that those who were lost to follow-up decided to see their pregnancies through, but this is unconfirmed. It is also possible that by excluding those who were pregnant at enrolment, women highly motivated to take PrEP were not given the opportunity. Given the heightened risk of HIV infection in women who become pregnant, being able to continue PrEP use during pregnancy may be a critical programming consideration.

At baseline, the TAPS cohorts had similar demographic characteristics (age, education, and place of origin) when compared to the recently described local FSW population in Johannesburg [26]. Yet, there was a higher rate of FSWs in stable relationships in our sample. This is likely a reflection of the group of FSWs accessing SWP clinics in general, as a similar profile was recently reported among SWP attendees not enrolled in the study [27].

The patterns of visits to the clinic for PrEP combined with the reported adherence would suggest intermittent use of PrEP while maintaining an overall engagement with services. Although we have only analysed self-reported adherence data in this paper, the data were collected at every clinic and pill collection visit, and women did not report perfect adherence and usually reported when they took 'PrEP breaks' suggesting a low levels of social desirability bias. Additionally, with no seroconversions among the PrEP users this does not appear to be an issue in maintaining a negative HIV status noting also the high use of condoms with clients. Reassuringly, there was no observed change in reported consistent condom use or number of partners in the last seven days over time in the study. STI episodes were fewer in the duration of the study compared to baseline for both arms. This latter finding, combined with the results of rigorous and consistent data collection on condom use over time with all sexual partners, suggests that the women who remained in the study may have been improving their attention to prevention through engagement in the study. This finding makes for an interesting comparison with other completed demonstration project studies among MSM where moderate increases in STIs during the study suggest slight reductions in condom use [28].

Finally, we estimated a total cost for both PrEP and early ART per person-year to be in the same order of magnitude as recently published estimates [29,30]. The higher TAPS costs for early ART compared to those included in the South African Investment Case for HIV and TB reflect the TAPS programme procedures, service utilization, and staff costs which are likely to be lower in routine services [30].

Limitations

Firstly, no comparison arm was included, limiting the ability to assess effectiveness of integrated services, as it would not have been ethical to maintain comparison groups with no or delayed access to interventions shown to be effective [31]. Secondly, efforts to replicate healthcare delivery through an integrated service were affected both by regulatory (dispensing from a pharmacy and medical officer assessment of adverse events) and ethics committee

(informed consent administration) requirements. However, we expect the removal of these requirements would improve rates of uptake and retention.

In addition, the National PrEP and early ART pilot in South Africa started 1st June 2016. After its initiation, this pilot could have influenced the uptake of the interventions for those FSWs approached for enrolment in TAPS. Conversely, it could have influenced retention within the programme for those FSWs for whom the follow up period overlapped with the provision of the national pilot. The TAPS clinics were the only providers of PrEP free of charge to FSWs in the public setting and required informed consent to access the interventions as part of a research study before the national rollout, where all services were also provided at no cost to clients. Furthermore, the implementation of PrEP as part of the national programme meant that PrEP could be viewed as a standard of care and therefore more normalised from the population's perspective. Since PrEP was no longer considered experimental after 31 May 2016, we expected that women would think about PrEP differently, which could have affected uptake and retention in TAPS. For example, as the programme was scaled up in the initial 11 sites (including in the two TAPS sites), we became aware that some of the TAPS participants opted to collect their PrEP from the mobile clinics in Pretoria, rather than coming to the fixed clinic where TAPS was located.

Finally, we do not have data on the women who did not come back to the study, and the adherence and sexual behaviour data are self-reported, increasing the possibility of bias. Unfortunately, drug level analyses of use in the PrEP arm were not available at the time of writing. However this will be presented in a more in-depth analysis in a subsequent publication. Additionally, the data reported are based on populations of FSWs in two specific urban settings, possibly limiting generalisability.

5.3.6. Conclusion

The findings from TAPS informed the set-up of the national rollout of PrEP and test and treat for sex workers. This analysis shows that PrEP and early ART can be aligned with existing health service programming for FSWs safely, without significant behaviour change, and with high rates of uptake for both interventions, with expected cost reduction in routine settings at scale.

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Declarations

Dr. Michelle Moorhouse and Prof Francois Venter declares receiving honoraria from Gilead for giving talks, and for participating on a PrEP advisory board. The other authors declare no conflicts of interest with regards to this study or publication. Drug supply for Truvada was donated by Gilead, and Atroiza was donated for HIV treatment by Mylan.

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Author contributions

RE, GBG, WDFV, and HR conceived of and designed the study. RE led the daily oversight of the study including data collection and the qualitative research component. GBG led the quantitative evaluation components, costing and modelling activities. WDFV is the lead senior clinician on the study; WDFV and MM provide clinical oversight and technical support. HR maintains oversight and support as Principal Investigator. NN, JM, RB manage daily activities in both clinics. NN manages data collection and cleaning processes. MACE and GBG designed and conducted all costing studies. GBG led statistical analysis of all data, with input from RE. RE and GBG drafted the manuscript with input and contributions from all authors.

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5.3.8. Supplementary Material

Table S6: Sexual behaviour over time by partner type: consistent condom use and number of partners in last seven days.

Consistent condom use		baseline			3mo			6mo			9mo			12mo		
Arm	partner type	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
PrEP	main partner	47	144	33%	25	62	40%	13	41	32%	14	34	41%	7	27	26%
	casual partner	14	22	64%	5	6	83%	4	7	57%	5	5	100%	3	4	75%
	occasional client	181	181	100%	78	78	100%	54	54	100%	38	40	95%	33	33	100%
	regular client	179	180	99%	80	82	98%	58	59	98%	49	50	98%	31	31	100%
Early ART	main partner	27	91	30%	38	72	53%	29	66	44%	33	67	49%	19	41	46%
	casual partner	16	20	80%	12	12	100%	11	12	92%	9	10	90%	6	6	100%
	occasional client	100	101	99%	84	85	99%	68	69	99%	66	66	100%	45	45	100%
	regular client	124	125	99%	84	84	100%	69	71	97%	69	69	100%	45	45	100%

Number of partners		baseline		3mo		6mo		9mo		12mo	
Arm	partner type	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
PrEP	casual partner	0,7	1,1	3	3,2	1	1,5	1,4	1,1	1,5	1,3
	occasional client	17,5	21,8	13,9	13,2	23,2	32,4	24,7	31,9	25	22,1
	regular client	22,9	21,1	12,9	10,3	8,3	7,9	9,1	8,9	10,7	9,4
Early ART	casual partner	1,1	1,6	1,75	2,1	1	1,3	1,5	0,8	0,3	0,8
	occasional client	10,5	10,6	10,4	9,6	14,2	15,8	12,5	10,7	14,4	12,7
	regular client	20,7	20,1	12,7	9,9	7,9	7,4	10,8	10,1	12,4	8,5

Table S7: Sexually transmitted infections: episodes over time.

	GUD	Genital warts	Herpes	Vaginal candidiasis	Vaginal discharge	Abscess	PID	TOTAL
				PrEP				
Baseline	1	4	1	7	3	0	1	17
month 3	0	0	0	0	3	0	0	3
month 6	1	0	0	1	1	0	0	3
month 9	0	0	0	0	1	1	0	2
month 12	0	1	0	2	2	0	0	5
month 15	0	0	0	0	0	0	0	0
month 18	0	0	0	0	0	0	0	0
month 21	0	0	0	0	0	0	0	0
				Early ART				
Baseline	1	5	4	6	7	3	3	29
month 3	0	0	1	0	4	1	0	6
month 6	0	0	0	3	0	1	1	5
month 9	0	0	0	1	1	1	0	3
month 12	0	0	0	0	2	0	0	2
month 15	1	0	0	0	0	0	0	1
month 18	0	0	0	1	1	0	0	2
month 21	0	0	0	0	0	0	0	0

Table S8: Self reported adherence over time (% of participants reporting taking medication every day).

	n	N	%
PrEP			
Baseline	-	-	-
month 3	81	95	85%
month 6	52	66	79%
month 9	40	57	70%
month 12	32	38	84%
month 15	18	24	75%
month 18	21	22	95%
month 21	13	16	81%
Early ART			
Baseline	-	-	-
month 3	98	103	95%
month 6	77	84	92%
month 9	81	86	94%
month 12	56	60	93%
month 15	31	31	100%
month 18	35	36	97%
month 21	29	31	94%

6.0 Chapter 6: Individual perspectives of PrEP use among FSWs in TAPS

6.1. Introduction

Chapter 6 is the final results chapter and addresses the research question associated with PhD Objective 5: *What are the perspectives and lived experiences of FSWs taking up and using PrEP in South Africa?* This question examines women's specific experiences of using PrEP. In a sense, the analysis and results presented here are coming full circle to the results produced in the systematic review, and extends this literature with PrEP-related experiences of FSWs in South Africa.

The experiences of using PrEP presented in this paper are some of the first to be reported among FSWs worldwide. The hope is that this paper will help to provide insight into why and how women will use PrEP, or reasons that they might not, within the context of sex work. Within the TAPS project, these data were captured through in-depth interviews with a selection of the study participants. These were designed to be conducted in a serial fashion with each selected participant at three time-points over the first nine months of PrEP use and/or study participation. Note that participants were not required to stay on PrEP to remain in the study, but were allowed to cycle on and off according to their needs.

These findings support the notions of applicability and acceptability as women were asked to reflect on their experiences with and perspectives of PrEP use, including how it fit into their lives, how they made meaning of PrEP, and their interactions with the services. This paper is also a reflection of the "fruits" of the formative work described in Chapter 3 where PrEP applicability was explored from a programming perspective, as well as the acceptability of the planned intervention presented in Chapter 4's presentation of FGD results.

By way of additional methodological background, in addition to what is presented in the paper, the IDI guides were developed using the MSEM framework adapted for this PhD and presented in Section 1.11.3. The VOICE C guides were used as a reference for design and formatting (1). IDIs were analysed using thematic analysis as defined by Braun and Clarke (2). They define thematic analysis as "…a method for identifying, analysing, and reporting patterns (themes) within data". This approach to thematic analysis features a six-phase process: familiarisation with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and finally producing the report. This particular

approach was chosen over others, such as grounded theory (3) or interpretive phenomenological analysis (4), because the aim of this research was to categorise and understand findings, not to develop a new theory, and thematic analysis provided a flexible, yet effective means of accomplishing this. The theoretical position of the analysis took a contextualist approach, meaning the analysis reported on the experiences and realities of the participants as well as how societal discourses and the external environment influence how the participants make meaning of their realities.

Additionally, the IDIs were conducted at three time-points at 3, 6, and 9 months of participation in the study. This is explained in more detail in the paper, however, the reason for choosing the serial IDI approach was to allow for developing concepts around perceptions and experiences of PrEP use over time, and in depth. In this paper, the focus is on the themes arising from these IDIs, rather than only focusing on the change over time given that the latter would have limited the analysis to change, potentially diminishing the depth of theme exploration.

Transcripts were simultaneously translated and transcribed, then uploaded into NVIVO software for coding and analysis. Overall organizational categories were initially developed according to the social-ecological framework used in the IDI guide, to help categorise the data into smaller, more manageable pieces given the serial nature of the interviews and volume of data. From this point, themes were derived in an iterative fashion by reviewing the data, assigning codes, comparing codes across the data and refining until a set of codes were consolidated and themes derived in relation to the research question. This process was performed by two researchers independently and then compared and aligned into a unified coding framework. Once all data were coded, findings were synthesized to explore commonalities and differences across the three IDI time points as well as across participant perspectives. The longitudinal analysis used a trajectory approach which focuses on understanding individuals' experiences over time (which was the aim of these serial interviews), as compared to a recurrent cross-sectional approach which usually assesses two time-points and is used on more of a cohort level (5). The analysis examined the data on a semantic level describing participant experiences as reported, as well as interpreting these experiences to uncover underlying ideas and concepts, much like the process undertaken in the meta-ethnography approach to the systematic review.

Additionally, as described in the previous chapter, TAPS enrolment took much longer than originally anticipated. This was due to several unforeseen issues with local eruptions of xenophobic violence and student unrest near the clinics as well as delays in launching the Pretoria clinic. While the original 12-month recruitment and enrolment phase of the study was extended, the project did not enrol the original target of 400 women on PrEP. This affected the participation in the IDI component of the study which was planned based on the original TAPS target. The aim was to enrol a random selection of up to 10% of participants in the IDIs (which would have been up to 40 across the two sites). This was planned instead of using purposive sampling due to the large number of anticipated enrolees and according to the sample selection method used in studies with similarly larger sample sizes, for example in the VOICE and MDP 301 studies (1,6). Unfortunately, by the time it was clear that TAPS would not reach its target of 400, it was too late to amend the sample selection method, and therefore the sample size remained aligned with the enrolled PrEP arm which reached 219 participants. Additionally, some women who signed up for the IDIs were lost to follow up, and though the sampling method was calibrated to select more than 10% to account for attrition, more were lost than the over-sampled selection. Perhaps a reflection of the vast difference in HIV treatment programming requirement versus those for prevention, there were many more women in the early ART arm of the study who participated in the IDIs, even though there were just over half the number enrolled in the cohort.

The paper presented in this chapter reports on and analyses the first set of salient findings from a rich data set. In order to conduct a deep dive into themes around PrEP uptake and use, this paper focuses only on the PrEP participant's perspectives (and does not include the women taking early ART). Many more qualitative data were collected through the course of TAPS which fall beyond the scope of this PhD. Additional papers will be forth coming combining the PrEP and early ART user data, and including clinic observations conducted over time along with provider discussion group data.

The information and consent form is attached in Appendix xi, as well as the three IDI guides which are attached in Appendix xii.

This paper is planned for submission to the journal Social Science and Medicine.

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Student	Robyn Eakle
Principal Supervisor	Peter Weatherburn
Thesis Title	An examination of real-world applicability and acceptability of oral pre-exposure prophylaxis (PrEP) for female sex workers in South Africa

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	JIAS
Please list the paper's authors in the intended authorship order:	Eakle, Robyn; Bourne, Adam; Mbogua, Judie; Mutanha, Nyaradzo; Rees, Helen
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I lead the design of the research, analysis, and drafted the manuscript.

Student Signature: [redacted] **Date:** 5 October 2017

[redacted]

Supervisor Signature: _____ **Date:** 5 October 2017

6.3. The PrEP Life: female sex workers' perspectives on uptake and use of daily pre-exposure prophylaxis for HIV prevention in South Africa

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6.3.1. Abstract

Women remain highly vulnerable to HIV infection where in sub-Saharan Africa they make up 56% of all people living with HIV, and female sex workers (FSWs) face some of the highest HIV prevalence and incidence rates. Oral pre-exposure prophylaxis (PrEP) is a new HIV prevention intervention with the potential to stem the epidemic among populations at highest risk, such as FSWs. In these early days of implementation, end-user perspectives of actual use in 'real-world' settings are critical to the success of PrEP. This paper presents findings from serial in-depth interviews (IDIs) conducted with FSW participants during the course of the Treatment And Prevention for Sex workers (TAPS) Demonstration Project in South Africa. The overall aim of the interviews was to elicit feedback on the uptake and use of both an early antiretroviral treatment (ART) for HIV-positive and PrEP intervention for HIV-negative FSWs integrated into an existing, comprehensive health programme tailored for sex workers. This paper specifically explores the lived experiences and perceptions of taking up and using PrEP among FSWs engaged in the TAPS Demonstration Project. Interviews were conducted with randomly selected participants during their 3, 6, and 9 month clinic visits, which aimed to allow for observation of change over time in reported experiences of PrEP use. The thematic analysis primarily focuses on elucidating the broader perspectives and positioning of PrEP within women's lives.

This research provides insight into the risks and responsibilities that women perceive in their lives as prominent drivers in taking up and using PrEP, the ways in which women adopted PrEP to mitigate their risk or ameliorate these realities, and the characteristics of PrEP that they most valued, all of which are critical to consider within the context of implementation. Disbelief in the existence and/or efficacy of PrEP affected the motivation of women to come to the clinic and to maintain use. As one of the first reports of personal experiences and perspectives of actual use of oral PrEP among a group of FSWs outside of a clinical trial setting, this research shows that it will be important to ensure accurate, relevant, and widespread messaging in communities to generate demand and support for PrEP. To achieve its potential as an HIV prevention game-changer, PrEP implementation requires in-depth, qualitative research to understand if and how it impacts on women's lives and what motivates them to take it up and adhere.

6.3.2. Introduction

The efficacy of dual drug combination (tenofovir and emtricitabine) oral pre-exposure prophylaxis (PrEP) for preventing acquisition of HIV in HIV-negative individuals has been extensively investigated and reported (1). PrEP has been incorporated into combined antiretroviral guidelines for prevention and treatment by the World Health Organization (WHO); is featured in HIV prevention guidelines in several countries and regions; and has been approved by regulatory bodies in at least 15 countries (2). In most countries currently implementing or testing the implementation of PrEP, the delivery is focused towards key populations at highest risk of acquiring HIV, following recommendations from mathematical modelling (3,4) as well as the WHO guidelines.

The focus on key populations stems from the relatively high cost of PrEP which would be mitigated by reducing new infections where they are highest, and from the need of these particular populations for new options to prevent HIV transmission when exposure occurs. Though not entirely termed as a key population, women in general are vulnerable where in sub-Saharan Africa they make up 56% of all people living with HIV (5). Female sex workers (FSWs) are a subsect of this population, who face some of the highest HIV prevalence and incidence rates (5). While FSWs were not included as a specific focus population in the oral PrEP efficacy studies (though they were inherently included in the studies of high risk women (6,7)), they are now the focus of many key population implementation studies in various phases of research across the globe(8). In South Africa, FSWs make up an estimated 91% of the sex worker population (9), and experience HIV prevalence rates as high as 72% in the greater Johannesburg area (10).

As the newest, proven HIV prevention method, PrEP represents an additional opportunity for protection among FSWs who often experience difficulties in ensuring condom use. Key factors affecting their vulnerability include ability to negotiate condom use, violence, poverty, and substance use (11–16). These factors, in addition to the distinctive structural issue of criminalization of sex work in most countries, make FSWs both uniquely suited for PrEP but difficult to design interventions for. In this regard, 'real-world' PrEP studies for FSWs thus far have centred on using an implementation science approach to determine how to integrate PrEP into existing service structures. Beyond the practicalities of implementation, however, is the need to better understand FSWs' individual perspectives of PrEP.

In these “early days”, end-user perspectives of actual use in ‘real-world’ settings are critical to the success of PrEP, and will ultimately determine the fate of future programming. This paper presents findings from serial in-depth interviews (IDIs) conducted with FSW participants during the course of the Treatment And Prevention for Sex workers (TAPS) Demonstration Project in South Africa. This sample represents one of the first set of FSWs to take up PrEP and report on individual perspectives of actual use. The line of inquiry was situated within a holistic approach based on a social-ecological framework, denoting reflections on the real and practical, rather than theoretical or trial-based use (17). This research provided the opportunity to examine motivations for and barriers to uptake, as well as what the women most valued about their use of PrEP. Such data will help to inform social marketing and education campaigns to generate demand and encourage PrEP uptake and adherence.

The overall aim of the interviews was to elicit feedback on the uptake and use of both an early antiretroviral treatment (ART) for HIV-positive and PrEP intervention for HIV-negative FSWs integrated into an existing, comprehensive health programme tailored for sex workers. This paper will specifically explore the lived experiences and perceptions of taking up and using PrEP among FSWs engaged in the TAPS Demonstration Project.

6.3.3. Methods

The qualitative research presented here was completed as a component of the TAPS Demonstration Project which was an implementation study designed to assess whether it was feasible, acceptable, safe and cost effective to roll out oral PrEP and early ART as part of an HIV intervention to FSWs in two urban clinics (Johannesburg and Pretoria) in South Africa (4). TAPS was launched in March 2015 and completed in July 2017.

A selection of women enrolled in the TAPS PrEP arm were invited to participate in the additional IDI qualitative research component during their month 1 clinic visit. TAPS participants were selected using a random sampling algorithm set to select a sample of 15% of those enrolled with the aim of enrolling a sample of up to 10%. This was according to the original design which sought a total enrolled cohort of 400 women across two sites. Women who accepted were required to complete an additional informed consent process for participation in the IDIs at the month 1 visit, and were then scheduled for interviews to be held on or around their 3, 6, and 9 month clinic visits. After each completed IDI, participants were

given R50 (~4 USD) as travel money, however there was no other monetary incentive given in connection with TAPS participation.

Initial interview guides were developed based on findings from a systematic review of qualitative evidence on women's perspectives on use of female-initiated prevention products in sub-Saharan Africa (18,19), as well as results from formative research conducted in preparation for TAPS (20), including focus group discussions with potential users (21). The premise and structure of the interview guides were based on the Modified Social-Ecological Model (MSEM) designed by Baral et al (22) to facilitate a holistic and broad inquiry. In practice, we took the levels illustrated in the MSEM, and built questions expanding from an individual-level to the broadest level as the HIV epidemic. The first interview guide was then adapted slightly for the second round of interviews, based on findings from the first round. The guide for the third round was similarly developed. In this way, themes were linked to follow stories of product use over time, but also adapted to changes observed over time to capture relevant topics.

The overall aim of the serial interview (often called Longitudinal Qualitative Research or LQR (23)) approach was twofold: 1) to see if and/or how women's realities changed over time with use of PrEP, and 2) whether they may become more open with the interviewer over time and provide richer narratives of their lives than those presented in the first interview, hopefully reducing social desirability bias in responses (24). While this method has been more prevalent in cancer-related research (23), it has more recently been employed in qualitative components of PrEP-related trial research (25). It should be noted, however, that the change over time is not the primary focus of this particular paper as it would have limited the exploration of themes to those in which change over time rather than allowing for a broader exploration of the data. It would be difficult to fully comprehend the change over time in this particular research without first looking at broader perspectives and positioning. Instead, this aspect will be examined in further detail in a future publication likely combining PrEP and early ART, however, it will be presented here as it relates to the key emerging thematic findings. IDIs were conducted in the participant's preferred language, usually a combination of local vernacular and English, and lasted up to 1.5 hours. Interviews were later translated and transcribed simultaneously by research assistants into English.

Analysis of the data began with development of a coding framework created separately by two researchers and then compared. A final framework aligning codes was developed and employed in 100% coding by both researchers of all transcripts. The framework and transcripts were uploaded and coded in QSR NVIVO 10™. Each round of interviews was coded in a separate database using the same coding framework.

After coding was complete, the two researchers compared findings and discussed any differences in coding to align results. This process was completed first, before the analysis of the serial aspect of the data. Thematic analysis was led by the first author, using the Braun and Clarke method (26). This approach involves a six-phase process: familiarisation with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and finally producing the report. In this regard, we adopted a contextualist position, where the analysis aimed to report on the experiences and realities of the participants as well as how the external social environment influenced how the participants make meaning of their realities in relation to PrEP.

All interviews were included in the analysis, even though there were not complete sets of three rounds for each participant. For those participants with second and third IDIs, change over time was explored by comparing the coded data associated with the prominent themes emerging from the initial analysis across the time points for each participant. This is called a trajectory approach, and was chosen since the aim was to take into account "individuals' experiences over time" (27). As there were fewer second and third round IDIs and the change over time was confined to the themes included for this analysis, it was possible to employ a simplified matrix approach and compare results worksheets (developed in Microsoft Word) for the three coded databases by hand. This was conducted independently by the first and second authors, and then findings were compared and found to have few discrepancies which were resolved.

Ethical considerations

All women participating in the IDI component of TAPS completed both the main TAPS study and separate IDI informed consent processes. The entire TAPS study was reviewed and approved by the Wits Human Research Ethics Committee (reference number: 140502), and the IDI component was also reviewed and approved as part of a PhD project by the London School of Hygiene and Tropical Medicine (reference number 10102). In addition, following any reports

of violence during the course of these IDIs, participants were offered relevant assistance, medical or otherwise, as needed.

6.3.4. Results

From those invited across the two sites, 18 women from the PrEP arm agreed to participate in the IDIs, 11 in Johannesburg and 7 in Pretoria. Following the first round, 10 women completed the second round of IDIs (4 in Johannesburg, 6 in Pretoria), and 6 completed the third round (1 in Johannesburg, 5 in Pretoria). This dropout relates to the overall rates of loss to follow up across the larger TAPS study (28). In total, data from 34 interviews were coded and are included within this analysis.

The ages of the PrEP IDI participants ranged between 23 and 40, with 10 between the ages of 23-30, and 8 between the ages of 31-40. None of the women were married, though nine of them had a steady partner, three of whom lived with their partners. A majority of the women were originally from Zimbabwe (n=12), one from Lesotho, and the rest from Gauteng, Mpumalanga, and Eastern Cape provinces in South Africa. Most of the women had at least some high school education, with three only having completed primary school. Finally, most of the women worked in brothels (n=12), while the rest worked on the street or in other less formal settings such as vacant lots.

The IDIs aimed to situate PrEP within women's lives, including every day worries, relationships with family, friends, and partners, caring for children, and navigating their working situations. The data presented here fall into themes describing their perceptions of risks and responsibilities and how PrEP fit into their lives, their experiences of PrEP use, and reflections on related interactions with others. These data reflect both a practical implementation (or public health) perspective of services and lived experiences. Each participant quote is labelled with a pseudonym, the location (JHB = Johannesburg; PTA = Pretoria), and the IDI number (e.g. first, second, third round).

Positioning PrEP in the wider context of women's lives: risks and responsibilities

Each of the IDIs began by exploring women's personal realities: how they were feeling, their worries and concerns, and their everyday meaningful experiences beyond HIV or safer sex. It is within this broad context that PrEP was considered and enacted. Emerging as one of the strongest themes among and across the interviews was women's articulations of risk and

personal responsibilities. Risks arose from their jobs in sex work resulting in poor health from STIs or HIV, or from violence which was common both in sex work and the inner cities in which they lived. There were also risks from main partners where condom use was limited. Responsibilities centred on money, needing income to support themselves and family members, as well as pursuing possibilities to improve their lives.

In one way or another, risks and responsibilities were universal, in particular around sex work: *" No I worry about the life that I'm living …. that until when will I be living this life of this job, if I could just provide for my children and I just pray that if I can get a job so that I can live a normal life as other people" (Maggie, JHB, IDI 1).* The burden of the job and its risks compared with the need to make money was a daily personal conflict: *"Yeah it was like something that is torturing me every day. And if I'm doing it, I will be telling myself I am digging my own grave here" (Nancy, JHB, IDI 1).*

As reflected in their demographic descriptions and voiced in the IDIs, most of the women did not have a sufficient level of education nor skills to apply for other jobs. Some were attending school during the time of the project and were supporting themselves and family members through sex work. *"I couldn't study because of the baby …. I had to run away from them* [school] *because they kept asking me questions. There is a teacher who I told because she had seen me by the street and I had to explain it to her why I did what I was doing" (Polly, JHB, IDI 3).* Polly acknowledged through the course of her interviews her desire for an education which conflicted with the necessity of working to provide for her daughter, as well as with her ability to come to the clinic. Her story represented a conflicting dynamic common to many of the women where they wanted and needed to continue engagement in care but personal responsibilities made this difficult. In her final interview she articulated her specific desire around future employment: *"I wanted to be a nurse but at the moment I can't" (Polly, JHB, IDI 3).* While none of the women in these interviews had moved to new jobs during this project, over the course of the IDIs ideas for the future became more tangible.

Many of the women were the sole providers for their families and felt the daily stress of supporting them resting heavily on their shoulders: *"Mostly the main thing which is worries me is my kids, that is the most worrying. Me at home, that I must fix everything no matter even to do this situation of work is because of the family thing, like my kids and my mom and my dad" (Brenda, PTA, IDI 1).*

The heavy weight of their perceived responsibilities emphasised a need to remain healthy and recognizing their risks as they related to the potential for HIV infection, was often a key factor in participants choosing to take up PrEP: *"A month I was only telling myself I will go, I will go, cause I will be busy. Jah I just told myself I'll go, I'll go next week, I'll go tomorrow …. Other people are afraid to hear their statuses mostly" (Mbali, JHB, IDI 2).* The fear of may have delayed interest in and initiation of PrEP for many of the participants, but it also seemed to contribute to a tipping point of motivation for those who joined the study and took up PrEP.

When asked about their main motivations for taking PrEP, almost all of them said the same thing - that it was to protect their health given the risks of their work: *"I am looking at the job that I am working its dangerous and it can give me diseases whereas I know that I am not sick" (Thembi, PTA, IDI 1).*

There was continuing underlying concern for the potential of HIV infection among these women, which remained even when using condoms and in their initial months of using PrEP. This was a pervasive sentiment. Condom breakage, a common occurrence, was a motivator to take PrEP: *"I was so happy and wanted to join* [TAPS] *immediately because I had a problem of condoms breaking. So now even so I know that when the condom breaks there is a medication I have taken to prevent HIV infection" (Maggie, JHB, IDI 1).*

Condoms could break through the general course of sex, or when men wanted to break them on purpose which was a common experience and an ongoing fear:

> *"Aaa what I can say about the pill is that the pill is good. It's ok cause it helps us from getting HIV, cause sometimes you meet very rough clients to an extent that the condom break. Some will be knowing that he is sick, he becomes rough with us because he wants the condom to break. Some guys are very, I don't know if I can say, they are rough or rude. I don't know" (Hope, PTA, IDI 1).*

Many women described PrEP in such a way that it could be considered a second-line defence, which made them feel safer: *"No it's the reason to drink prevention* [take PrEP] *because maybe if I wasn't taking it, then some clients bursts the condom and you don't know what to do. So when the condom bursts and the person has a disease you will not get it" (Sisi, PTA, IDI 3).*

This added protection also related to sex with main partners, where condoms were not usually employed. Women acknowledged condom use, or lack thereof, tended to define a romantic relationship versus sex with clients. This held true whether the women's partners knew they were sex workers or not. Navigating sexual relations with main partners was challenging, but PrEP gave women peace of mind with their partners when they couldn't be certain that they were the only lover in their partners' lives. Among women who had main partners (e.g. regular, steady, or non-paying), most admitted that they couldn't be sure they were in a monogamous relationship. PrEP was there to keep them safe within such relationships where condom use was less common.

(Dis)believing in a pill to prevent HIV

Over and above the motivation to use a product that could help to protect them from HIV and relieve some of the psychological burden in their lives, women needed to grapple with interpreting and understanding the stated efficacy of an entirely new technology. Given several decades of messaging that condoms were the only way to prevent HIV transmission during sexual intercourse, it was not surprising that the news of PrEP was sometimes met with disbelief: "*So but on my side I'm still deciding continue taking them or stop. I don't know now. Like what I was saying that people they wanna know if these tablets they are working or they are not working. I don't know. For that one I've no idea" (Royal, JHB, IDI 1).*

Missy related how some of her colleagues did not believe that PrEP was real, and how she and her sisters investigated the PrEP product:

> *"My younger sisters they do understand it because they even went online and check what is it that I am taking. And my friends, I explained to them. I even told them that it's coming on public they will take it although I didn't tell them that now its only sex workers that are taking this thing. I just told them that at the clinic they gave me this" (Missy, PTA, IDI 1).*

Reflecting on initial disbelief in PrEP came more often in later interviews. In her third IDI, Brenda reported how she had found colleagues in her room going through her bag. She worried they were stealing her pills, but she later found that they were actually trying to figure out what the pills were and whether they were real. They were all HIV-positive and couldn't grasp the concept of PrEP:

> *"It seems like, the way I heard it is, like they were showing everyone 'do you know how these tablets work?' And themselves they can't drink it …. I am still negative. They don't believe it. They said 'why you only? Us we are positive", you see" (Brenda, PTA, IDI 3).*

The other women in Brenda's workplace struggled to accept that, as a sex worker, Brenda could still be HIV-negative, therefore they grappled with the notion that she had been given pills to *prevent* HIV. They expressed genuine disbelief that preventive pills even existed. Brenda also admitted herself that she initially came to the TAPS clinic purely out of curiosity, not entirely believing that PrEP was real.

This confusion about where PrEP was real and actually prevented HIV persisted because it was only available to FSWs in special clinics and not widely reported on in the media, as one participant articulated: *"They ask me why it's not on the TV or on the radio? Why is it private, it's secretive? Jah they say if your clinic was real" (Nancy, JHB, IDI 1).* Some participants described their initial apprehension about potentially being guinea pigs for drug testing, which was usually laid to rest during the first couple months of participation. However, interactions in the community were a different story. When participants told others that PrEP was made of ARVs, it immediately signalled illness and HIV:

> *"Others were not happy for me they thought it was an ARV. And some understood, and some didn't, and with my family they are fine. I told him* [boyfriend] *but at first he could not understand that. I sat him down and explained it to him, then he understood but he then asked why is only for women" (Polly, JHB, IDI 3).*

Another participant recounted how she asked another organization working in her community about PrEP: *"So …. then I was asking her about the PrEP. She said they don't have. And they don't even know about it" (Brenda, PTA, IDI 3).* This general lack of knowledge in the community about the existence of PrEP made it more difficult to believe in on a personal level and then to convince others, especially when only provided to a select few, as Polly's boyfriend questioned in the earlier quote. Indeed, as the IDIs progressed, women suggested that promoting the message of PrEP to the broader community and making it available to others would help with supporting use by reducing the stigma around ARVs as being only for sick people: "*jah because ah the other friend once saw that medication and asked me about it …. But she didn't understand, she wanted to say that they are ARV" (Polly, JHB, IDI 2).*

Reconciling their own and others' confusion or disbelief around PrEP was observed across the second and third waves of interviews. This process seemed to contribute to a commitment from these participants to take PrEP, and also circled back to the motivation of managing and mitigating risk.

Disbelief in PrEP eventually dissipated for those who continued in the study, and part of eliminating the personal scepticism was by repeated HIV-negative test results. Motivations to test (and maintain PrEP use) were link to a firm desire to see continued negative results: *"I don't like it, but for the fact that, you guys need to see the results so I do it and I know that I am always negative" (Missy, PTA, IDI 1).*

Over time, personal belief paved the way for participants to prove to others that PrEP was real, since they were still HIV-negative. This elicited interest in PrEP from people outside of the study: *"Yes, friends and neighbours. Because I want them to get the same services I got. Like my friend she wants to take it and I told her about mine" (Polly, JHB, IDI 3).* After using PrEP for some time, women also wanted it for their main partners: *"I want to ask about this PrEP. I have a boyfriend. Is it possible for him to come and take this PrEP?" (Lebo, PTA, IDI 2).*

Finding health, control, and well-being in PrEP

Growing out of the acknowledgement of personal risks and responsibilities, as well as a confirmed belief that PrEP was real and playing a part in keeping women negative, was the notion of health and well-being reinforced by taking PrEP and through continuous engagement in care. This translated into a commitment to health, hope for the future, and a sense of strength and pragmatism in the present in relation to their work. Several women asserted their personal empowerment in taking PrEP, as Nancy told her friends*: "me I'm doing it, if you don't it's for your own good. I am doing this for my own life. Not for anyone" (Nancy, JHB, IDI 1).*

Regular clinic visits created a sense of assurance: *"No its good coming here 'cause you will be knowing your health. Unlike just sitting, you are just sitting you don't know what is going on. At least when you come here you will be knowing at least some" (Royal, JHB, IDI 1).* This, along with access to PrEP, created a level of added control in their lives, especially when armed with the knowledge that PrEP was not a forever regimen. This made it easier to rationalise use and

was equated with a potential end to sex work: "*We just talk about that one day when we leave sex work we will quit the tablets" (Pinky, JHB, IDI 1).*

Practically, women were given the option to cycle on and off PrEP through the course of the study, and they were counselled on if or how they might do so with the support of a clinician. Many women explained how they decided to cycle off on their own, and would come back for retesting to be able to restart PrEP a few months later. Some of these women related how they would take a break when they went back to their home villages or if they stopped sex work for a time, which seemed again to contribute to a discourse of enhanced control that ran through many of the transcripts.

Beyond control specifically, however, taking PrEP emerged from analysis as a source of positivity, stemming from an underlying feeling of safety: "*I feel …. happy. I feel great taking Truvada. I know I am safe taking*" *(Anna, JHB, IDI 1)*. Healthiness and happiness was important and underscored by all of the participants in one way or another. Safety also denoted trust, often a synonym for control over women's positions in their realities as sex workers: *"Since I've been using this medication I'm feel myself like I'm healthy …. Mmm I'm just happy, just makes me happy and jah and I trust myself" (Polly, JHB, IDI 1).*

Some women felt that the pill was helping them beyond preventing HIV. In this regard, some of the participants reported previous feelings of illness which had dissipated: *"…what I discover is like my health is like normal, normal I don't feel pain like I'm shivering anytime like what I did last time before. Now I'm feeling a good health, a normal breathe" (Joy, JHB, IDI 1).* They also reported overall relief from less concrete symptoms, which were more akin to general sensations: *"'Cause sometimes I normally used, I used to like sleeping …. but now sometimes, something is changing in my body. I used to feel like weak, in the morning when I'm waking up. I think it's helping" (Hilton, JHB IDI 1).*

When discussing how PrEP made them feel about sex, most women talked about the feeling of added safety, but not in a way which made them want to have more, or to have condomless sex. Most perceived changes in sex was related to their work. As one participant related:

> *"According to the rumours, they say when you take TAPS, eeh PrEP or ARV, your inner vagina it becomes more hotter like when mens are penetrating they will say you are hot, you are hot things … like most of my clients they say 'Yoh! You were so hot!' So I*

think that's what changed. I don't know because I cannot feel myself inside. No, I actually don't like sex (Missy, PTA, IDI 1).

Weight gain was a limited "side effect" (later attributed to feelings of well-being and not a clinical side effect), and tended to signify enhanced health and strength: *"Even the weight, I feel like it gives me weight when I am looking at myself" (Thembi, PTA, IDI 1).* While a small number of participants were not happy with the weight gain, for most who gained weight it was an explicit signifier of health, or a measure of personal fortitude and empowerment: *"Mm I think they [pills] make me strong. It's like now I, I am protected a lot since I use them, and me I can feel in my body that I am fine" (Lebo, PTA, IDI 1).*

Finally, there was a significant sense of altruism and a need to support their community among the participants who recognised value in PrEP and having access to it: "*I wanted this programme to help all of us, sex workers" (Anna, JHB, IDI 1).* This added to the sentiment of hope and the possibility of improving their perceived and physical positions in their work and life realities. Another participant felt that the act of offering PrEP to FSWs was a sign of change in how sex workers were perceived by wider society:

"…. I feel happy there's some of the government maybe is take care of people because they love everyone. They can't choice that this one is prostitute and what. They love us. They put us together as one people because they care. So I have proud that if I feel like I have a problem, I go there and tell them what I feel and I'm negative …. they are preventing us rather than to sick and die, leave our kids (Joy, JHB, IDI1).

Managing the practical complexities around PrEP use

Though not as prominent a theme in the interviews as compared to the others presented here, the practicalities of managing PrEP use and the activities relating to it were still important to consider. In particular were the practical issues of daily pill taking, managing personal relationships in relation to PrEP use, developing supportive structures, considerations around behavioural disinhibition, and managing the practicalities of clinic attendance.

Developing innovative strategies for pill taking was universal, including stashing a pill or two in a bra or a tissue in case of late or unpredictable nights, setting phone alarms, and placing the pill bottle in a routine location like next to a tooth brush. These were not always perfect. Like others, Mbali admitted to sometimes forgetting: *"…. we do forget 'oh today I didn't take my pills!'. Before I was forgetting, I don't wanna lie. Now I don't forget"* (Mbali, JHB, IDI 2). Often,

participants would admit when they missed doses or ended up sharing with someone else also taking PrEP to top up their stores when they couldn't make it to the clinic on time:

> *"We do share I don't wanna lie. You told us not to share, but if we run out we do share. We just told ourself it is one thing. We said how can we not share, but this is one thing. When I run out I can just say give me two. I will be drinking my sister's" (Mbali, JHB, IDI 2).*

Most of the women participating in second and/or third IDIs seemed to be more open or honest about struggles with pill taking, while others described becoming better and finding strategies for consistent pill taking. Some suggested, after taking PrEP for a while, that having an injectable would be better than the pill, to alleviate the burden of daily adherence, most likely related to their experiences with or knowledge of injectable contraception.

One way or another, support systems for pill taking were important in maintaining use. Family, friends, or partners could be a source of support: *"Jah like my sister we do take PrEP together, so when she is taking I take also" (Mbali, JHB, IDI 2).* Loved ones who were HIV-positive could act as a support system for taking PrEP: *"My sister is positive. So she is the one who say to me you must go and take" (Mandy, JHB, IDI 1).*

Others ended up losing family, friends, or partners over their participation in the study and PrEP use. This was an unfortunate development, but it also usually resulted in a reaction of asserting a sense of empowerment or control. For instance, Missy decided to stay in the study and lose her boyfriend who would not believe that she was taking ARVs for prevention, rather than give up taking PrEP:

> *"I don't have my partner anymore he dumped me because I am taking TAPS/PrEP and he doesn't even believe this …. He, he dumps me because I am drinking this medication which he thinks I am drinking HIV ARV …. Hee ee I did explain, the thing is he lack information too much" (Missy, PTA, IDI 1).*

Disinhibition, or discontinuing condom use while using PrEP, was not reflected among most of the participants. Only one woman admitted to sometimes giving more oral sex without a condom than before she started taking PrEP, and a few women spoke of how they had considered not using condoms on occasion. However, given that most still relied on condoms to prevent pregnancy, most of them were discouraged from condom cessation: *"I was scared because what if I get pregnant? So if I get pregnant I put my life risk" (Joy, JHB, IDI 2).* Others

asserted the importance of maintaining broader sexual health, and highlighted the important, but incomplete, contribution that PrEP made in this regard:

> *"I worry about my health. Because without my health I will not be able to provide for my family …. but I make sure that I prevent all of them. I prevent STI using condom, and prevent pregnancy again using condom and by eeh mmm using the injection, and I also prevent HIV by using PrEP" (Missy, PTA, IDI 1).*

Finally, personal treatment at the clinic made it easier to keep coming: *"I like the fact that when I come to the clinic they tell me I look nice, they remember me, and they will ask me what month am I here for. They will tell me go to this one* [staff member]*, go to that one" (Missy, PTA, IDI 1).* The feeling of the clinic was a big draw for participants in both locations: *"The study is a very good thing to attend and you feel comfortable and safe" (Maggie, JHB, IDI 1).* All participants related how the service at the clinic supported their PrEP use and attendance: *"…. because you guys are free, you are welcoming and one won't be shy to express and say what they came to the clinic for" (Joy, JHB, IDI 2).*

6.3.5. Discussion

This is one of the first reports of personal experiences and perspectives of actual use of oral PrEP among a group of FSWs outside of a clinical trial setting. This research provides insight into the risks and responsibilities that women perceive in their lives, the ways in which women adopted PrEP to mitigate their risk or ameliorate these realities, and the characteristics of PrEP that they most valued, all of which are critical to consider within the context of implementation.

The findings produced from this research are grounded within the MSEM framework, where personal views and factors interact with and are influenced by social and sexual networks, community, societal and public policy, and the HIV epidemic itself. While the findings were not presented within this framework, the components are visible within the themes where community perceptions of PrEP influenced personal beliefs and experiences of use, or where knowledge of the vast epidemic made it difficult to believe there were still HIV-negative FSWs left to take advantage of new prevention methods.

Disbelief in the existence and/or efficacy of PrEP was a prominent theme, which affected the motivation of women to come to the clinic (as reported by those in the IDIs), and also affected women trying to maintain use. When those around the users are constantly questioning

whether such a preventive product can be real, it may be difficult to continue use. This could speak to reasons for dropout in the larger TAPS study for which the primary, programmatic results have been presented (28). Indeed, targeting this PrEP intervention to a population at highest risk may have risked the trust in the product and its ability to prevent HIV as community education was not widespread. This disbelief was also a phenomenon seen in the VOICE-D sub-study and HPTN/ADAPT studies which found scepticism of PrEP efficacy to be a significant barrier to use (29,30). Both Normalization Theory (31) and the Diffusion of Innovations (32) speak to the imperative of community assimilation of interventions for successful implementation. Indeed, without belief in and demonstration of efficacy on a personal level (e.g. repeated negative HIV tests with PrEP use), little engagement can be expected. This was underscored by the participants in the IDIs in every round, and often raised ethical quandaries around not being able to provide others with PrEP. The clinic did, however, allow and promote couples testing as desired by the participants.

Risk, and risk perception (33), have been extensively researched and debated in regards to translating into effective HIV prevention uptake (34–36). Research published from the FEMPrEP efficacy trial found that women in the study who did not maintain PrEP use also did not accurately assess their own risk (37). In the TAPS study, the primary results suggest that the population accessing PrEP women may be at self-acknowledged high risk, which was confirmed repeatedly through the IDIs (28). However, it is unclear whether those who dropped out were accurately assessing their own risk or not, though one woman who dropped out of the PrEP arm early returned later with an HIV-positive result. The risks articulated in these IDIs, however, were directly linked to the dangers of sex work and the response to these was closely intertwined with the acknowledgement of personal responsibilities. In addition, these personal responsibilities could also contribute to women's abilities to maintain use if priorities for making money or going to school prevented them from making it to the clinic on time for visits and PrEP refills. At the same time, stress around condomless sex with main partners seemed to be reduced for some women who worried they might be at risk when partner fidelity was unclear.

While sex work can be a choice and many women have been empowered in their engagement in it (38), women in this sample of sex workers overwhelming felt that they currently had no options to transition out. Most transition programmes have failed because they don't offer women options to make enough money to meet their perceived responsibilities (39). In these

IDIs, women had mixed feelings about how to move on to other employment, with some asking for jobs in the clinic and others pursuing educations with the hope of empowering themselves to advance.

The notions of empowerment and control were underlying currents throughout the findings of these IDIs. While most of their worries remained constant throughout the progression of the interviews, there was also an alleviation of stress which occurred as PrEP efficacy became a personal reality. PrEP is not a magic solution to all problems, however, it started to symbolize hope and future prospects, as well as added safety, where women could view their business as business without as much fear, and sexual interactions with partners were less worrisome.

Interestingly, the findings in this paper at the thematic level are very similar to what has been published so far from qualitative research of PrEP use among MSM. Research published from an open-label PrEP study (following the iPrEX efficacy trial) presented relief from stress around the possibility of HIV infection and a sense of security as additional benefits of using PrEP (40). These feelings did not seem to change sexual behaviour, which from analyses conducted thus far and what was has been reported in our qualitative research, is also what happened in TAPS (28). Similar findings regarding the alleviation of fear around HIV were presented from another study of MSM in the United States (41). Encouragingly, this research suggests that PrEP use may provide sources of critical, constructive, and empowering HIV protection for those at highest risk of HIV without subsequent risk compensation, as was widely feared (40,42–45).

Not as many women returned for second and third IDIs as hoped, which is a risk with any longitudinal research and in particular with more transient populations such as sex workers. It is difficult to assess why participants drop out over time when they do not provide specific reasons themselves. However, based on what we learned here and what was learned in earlier research preparing for the TAPS study (20,21), it is likely that a combination of social dynamics around belief in PrEP and its efficacy (including stigmatization of taking ARVs as a sign of illness), personal risk assessment which may fluctuate over time, personal responsibilities which supersede clinic visits and participation in research, and potential issues with substance use probably contributed to retention. For these reasons and to further unpack the dropout seen in TAPS to help support PrEP programming, additional research is being considered to potentially interview women who were lost to follow up, to determine the reasons.

Despite the limited number of second and third round IDIs, the process of serial interviews enabled us to examine progression of thinking and feeling around PrEP use. In most cases, the participants became more committed over time, and discovered personal strength in their commitment, even if adherence was not always perfect. Their willingness to be more open about issues with product use grew over time, which was a benefit of this method. The practicalities of use were not the central themes for any of the IDI participants, however, women were able to share how they managed adherence or cycled off and on PrEP over time. One prominent component of managing PrEP use, which became more and more apparent over time, was the development of supportive structures for pill taking. Some women found support from partners, but many more had family members or friends who were already HIV-positive and could provide inside knowledge of pill taking habits. This reinforces the idea that synergies can be found among HIV-negative and positive populations, which may also help to destigmatise interventions.

Limitations

The study ended up only enrolling just over half the originally planned sample size, which therefore limited the range of perspectives possible to include. Additionally, we planned to capture perspectives of women using PrEP as well as those cycling off, however those women who cycled off rarely stayed in the study. The study sites were also limited to urban settings, therefore findings may not translate to other contexts. While these are clear limitations of this research, it should also be noted that the interviews did reach saturation of data, where personal stories did vary but themes were consistent across FSW accounts.

6.3.6. Conclusion

PrEP represents a valuable new HIV prevention option for women in sex work who are able to remain care. Risks and responsibilities were the main expressed drivers of PrEP uptake and use in these interviews, however, personal and community disbelief in the reality of PrEP efficacy challenged this. As PrEP programming is scaled-up, it will be important to ensure accurate, relevant, and widespread messaging is employed in communities to generate demand and support for PrEP use, even if use is to be focused for those at highest risk. PrEP could be one of the most significant game-changers in HIV prevention for the past 20 years, and requires this kind of in-depth, qualitative research to understand if and how it impacts on women's lives and what motivates them to take it up and adhere.

6.3.7. References

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7.0 Overall Discussion and Conclusions

The findings in this PhD represent lessons learned in one of the first implementation studies of oral PrEP for FSWs in sub-Saharan Africa. This body of research is part of the beginning of a new wave of HIV prevention programming as well as the culmination of more than 20 years of scientific discovery and product development now being taken to market. This PhD reviewed the qualitative evidence on previous research concerning HIV prevention products initiated and controlled by women, described the process and lessons learned in designing a new PrEP intervention, presented community perspectives of PrEP immediately before implementation, assessed key characteristics of women taking up PrEP, and explored the perspectives of a selection of women who used PrEP to elucidate the reasons for PrEP use and how it fit into their lives. Each section of research addressed the overarching aim of examining the applicability and acceptability of PrEP for FSWs in South Africa.

This chapter summarises and synthesizes the findings from this research by addressing each research question linked to the PhD objectives, discusses strengths and limitations, includes suggestions for future research, policy and practice, includes personal reflections on the research, and presents conclusions.

7.1. Summary and Synthesis of Findings

Objective 1: What are the motivations and barriers to uptake and use of female-initiated HIV prevention products in sub-Saharan Africa?

The systematic review in the form of the adapted meta-ethnography brought together data from many populations of women in different countries in sub-Saharan Africa and examined several products. Although not all of the products were successful in preventing HIV or getting to market, the qualitative research derived from all of the studies provided important lessons which can be applied to future product development as well as implementation of newly proven products. While much of the earlier qualitative research has focused on the acceptability of specific product attributes or specific aspects of motivations for use, such as the ability to use a product covertly for women, the analysis in this review found that core elements of sexual satisfaction, trust, empowerment and control were more important to women in terms of HIV prevention product uptake and use. These elements do not operate independently of one another and are mediated by other influences, such as product use in relation to the social environment where stigma and other people's perspectives may

influence uptake and use. Personal well-being, in terms of health and personal empowerment situated within the realities of women's lives, also interacted with the core influencing factors by mediating the ability to trust a product or a partner depending on how the prevention product affected relationships, for example. Risk reduction and efficacy, and product attributes played a more peripheral, but important role in how the products were perceived, especially in regard to initial acceptability. For instance, while covert use could be part of strengthening empowerment and control, this could all be suddenly removed by lack of trust from a romantic partner or if suspicion arose from discussion with friends or family that the product was actually designed to cause illness rather than prevent it. Effectively, the systematic review in Chapter 2 argues that all of these elements must be taken into account when developing and implementing a new HIV prevention product for women, or risk it not meeting the needs of the end-users.

The findings from this paper provided the basis for exploring a holistic approach to fill gaps in PrEP implementation knowledge through the entire process of designing, developing, implementing, and analysing the TAPS Demonstration Project. The design and development process was specifically built using an adaptive, grounded approach in order to allow for holistic, comprehensive thinking and responsiveness to the needs of the women who were potential study participants and PrEP users. Therefore, the elements from this review were built into the continuing lines of inquiry throughout this PhD and the larger TAPS project, also using the MSEM to situate the research.

Objective 2: What are the practical and contextual factors which might affect the uptake and use of PrEP among FSWs in South Africa?

With lessons learned in mind, the process of designing a PrEP intervention for FSWs in South Africa to be implemented and evaluated as part of the TAPS project was undertaken by examining all possibilities for modes of delivery, programming, end-user and stakeholder perspectives, as well as what was feasible. This was a learning process as well as a nearly simultaneous decision-making process. Additionally, final decisions often ended up very differently from where the research began. This was especially true for site selection, where the original plan was to choose three diverse sites from among the large network of sex worker clinics already supported by Wits RHI. However, after physically seeing the sites, talking to the clinicians, local DoH representatives, and FSWs, it was clear that the differences between sites were so vast, and sites spread so far apart, that having two sites closer together

where there were greater similarities was going to make for better management and measurable outcomes overall. The factors contributing to these differences were the types of sex work locales, continuous versus intermittent migration of the FSW populations, and social and economic factors, in addition to some sites not having adequate clinical facilities or links to appropriate laboratories, or support from the local health departments. These lessons were not only important for designing the PrEP intervention for TAPS, but also for the eventual government rollout which began on 1st June 2016 in South Africa.

In addition, through the process of this design exploration, it became very clear that PrEP and early ART should and could be implemented together. This viewpoint came from stakeholders themselves, who in early consultations underscored that bringing in a new prevention method, especially ARV-based, would be better accepted by the community if options were also available to those who were already HIV-infected. This was highlighted by representatives from other PrEP demonstration project country teams during an international sex worker stakeholder meeting on PrEP, where they described how PrEP could threaten the community's sex work market, and therefore early ART (or treatment as prevention as it was termed at that time) had to be a part of the mix (1). This was further supported by consultations in South Africa, where the argument was less about displacing the sex work market and more about ensuring unified messaging around HIV prevention (ARVs could offer protection if given to HIV-negative and positive sex workers). This was in addition to prioritising options for a population with the highest prevalence rates of HIV (2), and preserving an important ethical standpoint of not risking treatment for those who were already infected by appropriating budget and drugs to those who were not (3). The latter was a highly debated topic concerning PrEP before implementation studies were launched (4–6), and therefore one of the aims of the TAPS development and implementation was to demonstrate the synergistic feasibility of programming PrEP and early ART together, as well as the benefits to the community (7). While the larger answers as to how these synergies developed in terms of feasibility lie beyond the scope of this PhD, it was important to include here the existence of implementing early ART alongside PrEP, as PrEP could not be delivered in a vacuum, and indeed valuable lessons were learned from interactions with HIV-positive women who could represent a strong source of support for PrEP and PrEP users.

Objective 3: What are the community-level perceptions of PrEP in terms of acceptability within the context of imminent implementation among FSWs in South Africa?

In order to holistically approach the impending implementation of PrEP (and early ART), the FGDs conducted at the end of the TAPS formative research process and immediately before project launch combined both HIV-negative and HIV-positive women as well as discussions of both products. These discussions built on the findings of the systematic review and the earlier design process, where the questions posed in the FGDs began from a more general view of FSW's previous experiences with healthcare, what was important to them in terms of care, and how their social circles and lives interacted with services. This set the context of experiences in clinics as well as with the larger community, how partners and other loved ones may have influenced engagement in care, and how perceptions of the HIV epidemic may have fed into the participants' previous motivations for seeking care. This allowed for PrEP and early ART to be conceived of by the groups within these contexts and be able to discuss as a group how the interventions might relate, and work or not work.

Although both HIV-negative and positive women were combined in the FGDs, the paper presented in this PhD focused specifically on the groups' consensus regarding PrEP. The overall finding was that PrEP was highly anticipated and endorsed. Many of the women in the groups added their names to waiting lists for the study, and were anxious to know when PrEP would be available. Concerns voiced among the groups revolved around the possibility of discontinued condom use, issues with pill taking in relation to the ability to form adherence-related habits, and potential issues with substance use which are generally prolific throughout the sex worker community, mostly as a coping mechanism (8). Interestingly, women acknowledged (on their own) the potential for risk disinhibition and risks in rumours that could develop around fear of side effects, which have been concerns voiced in other studies and in the larger PrEP field (9–11). This connects back to the trust in product element, as well as in information circulating about a given product, illustrated in the systematic review. The fact that these issues were quickly recognised by potential future users, as well as those who might support those users, could provide some reassurance and signal to implementers that the community could handle the PrEP intervention given their keen insights and understanding of the likely complexities.

The normalization of PrEP was also highlighted in the FGDs as an important factor to consider in advance of and during implementation. A common thread through the discussions was the

stress which comes with the fear of HIV and being HIV-positive, which is accompanied by ARV treatment which has traditionally been a symbol of illness (12). From the participants' perspectives, with the introduction of PrEP came an opportunity to destigmatise ARVs since both HIV-negative and positive women would then be taking them. ARVs could then have the potential to become a symbol of wellness, and the inevitability of becoming HIV-positive and sick would no longer be a foregone conclusion for those who were still negative.

These insights were invaluable in tailoring the final messaging for the TAPS project, and helped to provide evidence of desire for PrEP among FSW communities in South Africa to the international community, which was not convinced that PrEP would be positively received at the time (1). This research created a logical bridge from formative research to the actual implementation of PrEP in TAPS.

Objective 4: What are key characteristics of FSWs who take up and use PrEP?

The key demographic characteristics of women taking up PrEP in TAPS, as defined by the literature and South African context (13–17), were: age, relationship status, level of education, place of work, and place of birth. The majority of the TAPS study population taking up PrEP was between 21-30 years of age (with a full range between 18-60 years); married, living with, or had a steady partner; worked in brothels; and were born in Zimbabwe. While there was not a population-based sample with which to compare both Johannesburg and Pretoria TAPS demographics, the characteristics of the women in the Johannesburg sample were similar to those in a recent analysis of the Wits RHI Sex Worker Programme data (18), and the SAHMS study (2), with one exception to the latter: there were fewer single women in TAPS than in SAHMS (which was a much more diverse sample than the programme data). While this is likely a reflection of women already attending the existing sex worker clinics, it may also be an indication of accurate risk perception where condom use was reportedly low with main partners throughout the course of the study. This links with discussions among the FGD participants, many of whom said they had been infected with HIV from their boyfriends or husbands. Indeed, some of the women in the FGDs had asked whether PrEP could be given to married women in general since there were not always familiar with their husbands' whereabouts, or their extra-marital sex.

Another interesting finding was that women had higher rates of STIs at the TAPS baseline, than throughout the rest of the study, which suggests that condom use was not replaced by PrEP

use or at least that women were paying more attention to general prevention than at the start of the study. It is important to take into account that this effect is difficult to definitively measure statistically due to the large drop off over time, therefore diminishing data points. However, directionally this is a positive finding for those concerned with disinhibition in a high-risk population where monetary incentives to drop condom use with clients have been hypothesized to have serious, deleterious effects (e.g. rising rates of STIs and unwanted pregnancy) (19,20).

These findings are also well situated within the MSEM framework where individual, social and community, as well as epidemic related factors interact and start to develop a picture of the PrEP user among FSWs in South African urban populations. These characteristics, combined with the FGD data and the qualitative findings from the IDIs, present a narrative of self-selection and risk awareness among these populations which will be valuable to consider using the holistic perspective of a social-ecological framework during scale-up.

Objective 5: What are the perspectives and lived experiences of FSWs taking up and using PrEP in South Africa?

The findings from the IDIs contribute a critical piece in developing the larger picture of PrEP use among FSWs in urban South Africa as one of the first sets of data on PrEP use among FSWs outside of a trial setting. This research took place in actual sex worker specific, primary health care clinics, and these perspectives help to solidify important considerations around risk perception, motivations for uptake and use, as well as barriers to uptake and use arising in the complex context of women's lives. These notions began development in the systematic review, and progressed with each step of the PhD until they could be explored in further depth with the serial IDIs.

Over the course of 34 interviews, the prominent theme of daily risks and responsibilities emerged as an important reason to seek PrEP and stay healthy, but these aspects could also contribute to women's abilities to maintain use if priorities for making money or going to school prevented them from making it to the clinic on time for visits and refills. Initial and continued scepticism of whether PrEP was a real product and, if it was, whether it really prevented HIV was also a prominent and consistent theme discussed throughout the IDIs. This disbelief permeated women's minds when initially considering PrEP, and even after they first started taking it leading some of them to admit they were not taking it all the time. Such

scepticism also spread throughout the community, where many colleagues and friends refused to believe there was such a thing as a pill to prevent HIV. One woman's partner left her because he could not believe that PrEP really existed. Instead he was convinced she was HIV-positive. This element plays back into the dynamics of trust, both in the product and among people, which came through as a core construct in the systematic review. The constant questioning of PrEP existence and efficacy may have contributed to the less than ideal recruitment and retention in the study, which reinforces a need to focus on educating key populations on these points in any future scale-up and rollout.

Following on from the notion of disbelief is the need for normalizing oral PrEP as a viable and accepted product within the sex worker community, but also among the larger social environment within which use takes place. Once oral PrEP is more normalised, then the disbelief will dissipate and create a more supportive environment for PrEP use. Additionally, there is an opportunity for destigmatizing ARVs as a symbol of illness, if both HIV-negative and positive women are using them. This was underscored by participants in the IDIs who wished that more people could have access to PrEP, both because they needed the prevention option and because then it would help them to understand exactly what PrEP is.

Interestingly, while the notion of sexual satisfaction with PrEP use was probed in the IDIs, most women talked about the reduction in fear of HIV over time with continued PrEP use as a source of contentment, and in actuality, a source of personal empowerment through control over their own safety. Some similarly acknowledged a reduction of stress around condomless sex with main partners where not using a condom defined the romantic relationship, however there was still worry from the women's perspectives of potential exposure to HIV with unknown partner fidelity.

The change over time captured by the serial nature of the IDIs was not the sole focus of the paper included in this PhD, as it would have limited the exploration of themes which do not necessarily feature change. However, the serial IDIs did support this particular analysis in revealing the aspects within the themes explored here which did evolve, such as the ability of women to talk about PrEP more openly as they became more comfortable with it themselves. This is clearly a feature of the women in the study who were committed to the study, to engaging in preventive care, and to providing feedback. A key consideration moving forward

will be how to build on these participant (or clinic client) attributes in scaled-up prevention to encourage and support more women at high risk of HIV to also engage in care.

The MSEM framework was useful in organizing the research questions employed in the IDIs as well as ensuring the approach was holistic and allowed for discussions to span across the framework spheres (see Introduction Section 1.11.3). This research did not intend to prove or disprove the validity of the framework (as one might with a theory) and did not find that particularly significant changes would have been necessary for it to fit better with the data. Potentially, dynamics around poverty and substance use could be imbedded to add depth, as these may have mediated the ability to continue PrEP use according to participants in the IDIs, as well as experiences from the larger TAPS study. Perhaps the greatest utility of the MSEM more broadly is the principled notion of taking into account the element of risk and the disease epidemic in addition to the social-ecological spheres of influence which further prompted this research to add FSW specific adaptations as well as the element of HIV prevention to create a framework incorporating nuance. Nuance is often omitted from such frameworks or theories, and usually the source of criticism for many of these in the broader health promotion literature (21).

7.2. Strengths and Limitations

The primary strength of this research is that it is one of the first to investigate and report a progression of thinking and perspective from conception of the intervention for women to individual experience of PrEP use among FSWs. While many papers published in the last several years have examined the theoretical acceptability of PrEP among key populations, this body of work represents some of the first research to examine the real-life uptake and use of the product among female sex workers. This progression of research from start to primary results of intervention implementation is another important strength of this research, where each step informed the next in a cumulative fashion to develop a significant knowledge base.

This work also contributes an end to end narrative of intervention design and development illustrating the depth and scope which can be considered within the Implementation Science paradigm. As discussed in Chapter 1, traditional definitions and approaches have centred on top-down approaches, where the nuances of programming and delivery inclusive of target population perspectives are not always accounted for or at least reported. In the research presented here, this was the starting point and fulcrum from which all work proceeded,

allowing for depth in design and development of the PrEP intervention which will serve as a source of learning for continuing scale-up.

There are also several limitations to this research. First is that, while every effort was made to preserve a 'real-world' environment and experience for participants in TAPS, it was still a research study and carried with it certain research related attributes which could have swayed participant experiences in a variety of ways. For example, the informed consent process was lengthy due to national requirements when distributing pharmaceuticals in a research study not yet registered (as Truvada was for use as PrEP at the time TAPS was launched), and may have deterred women from enrolling (22). There were also questionnaires and most likely more frequent clinic visits than will eventually become the standard in South Africa and elsewhere, which would detract from the 'real-world' implementation aspect where lessons learned may not always be applicable to occurrences in a broader programme setting. The quality of care in TAPS was also different from what is typically received in general public health clinic settings, where nurses were able to spend more time with participants and they had regular access to a doctor which is also not always typical, but was necessary for ensuring participant safety in PrEP use. The quality of care, though not discussed in-depth in this PhD, was often cited by participants as an important part of their continued participation in the study and may have influenced PrEP use. This aspect will be explored in greater detail in additional, future publications.

While this PhD took a relatively broad, holistic approach to the lines of inquiry developed, there were many additional questions which were not addressed. For instance, cost-effectiveness and intervention impact, as well as retention in TAPS and clinical outcomes, were not included here as they were beyond the scope, however they are important factors which would further complete the implementation picture. These aspects were investigated as part of the larger TAPS study, however, and will be presented in separate, forthcoming publications. Additional areas not covered, but highly relevant to this work are the issues of criminalization of sex work in South Africa, migration, and violence. These are slightly touched upon here, but were not explored in great detail in this work.

The TAPS project did not reach the 400 PrEP participants intended as the original enrolment goal for the study. This was due to many factors including local unrest making it impossible to get to the clinics, as well as issues with launching the Pretoria clinic due to local pharmacy

approvals. These were 'real-life' experiences which would affect any health programme and were taken into account as part of implementation research outside of a clinical trial, however they also contributed to a reduced sample size by almost half thereby also reducing the number of women included in the IDIs. This may have resulted in skewed sample demographics and qualitative perspectives, although comparison with other samples seems to confirm that the former was not the case (2,18).

Finally, the populations included in the majority of this research, except for the systematic review and design process paper, were concentrated in specific urban locations within the same province in South Africa. Throughout the design process, it was clear that no two sex worker locales are the same, and while there can be similarities upon which health programming can be built, it is the differences which should be meaningfully considered. Therefore, the results of the latter part of this research may not be entirely generalizable to other settings, however the research questions are likely to be relevant.

7.3. Next steps and Future Research

All of the research contained within this PhD has already been shared in one form or another (publications, presentations, or data sharing with stakeholders) to help develop learning around PrEP implementation to progress the scale-up process in South Africa, in the African region, and internationally. The systematic review findings have been presented at the 2014 AIDS conference in Melbourne, Australia (23), and also at several meetings focusing on exploration of data to support decision making on future prevention product and guideline development. The TAPS design directly influenced the designs of several studies in sub-Saharan Africa and India through a multi-country PrEP working group. The TAPS data and expertise developed during the course of the study provided the foundation of the national South African guidelines for PrEP and test and treat for sex workers which was launched in 2016 (24). In particular, near real-time feedback was provided to the NDoH in terms of lessons learned in managing recruitment, screening, enrolment, and retention as well as the synergies of implementing PrEP and early ART together. Additionally, this expertise and data were used to develop national PrEP training programmes for providers.

Next steps will include further analysis of the early ART and larger service delivery qualitative data from the FGDs and IDIs, as well as additional analyses of the clinical, demographic and behaviour data, cost and impact of TAPS. These will all be shared with central databases as

well as published for broader comparison and learning across studies and contexts to better develop PrEP interventions throughout the world. Additionally, the results from the research can provide data for developing the current national PrEP interventions, particularly in South Africa where little community-based preparatory work was conducted in advance of the launch of the initial national pilot. An evaluation of the pilot and subsequent expansion of the PrEP programming is planned, and earlier findings from this PhD have fed into the design of research tools which could be further updated. These findings are also supporting the development of pilot (government-led demonstration projects) in Swaziland which are focusing on higher risk populations such as sex workers, but striving to expand the opportunity to try PrEP to a wider audience.

In addition, research is being considered to follow-up with participants who were lost to follow-up in TAPS, as well as tracking those who were captured as informed about the study but did not come to the clinic for screening or enrolment to explore reasons for lack of uptake. This would help to balance the understanding of whether the main reasons were really the lack of belief in PrEP or personal responsibilities preventing clinic attendance, or whether there were other factors not immediately apparent which could be addressed in scale-up.

In the medium and longer-term, the lessons learned in this PhD and the larger TAPS project can be used to help with conception of new ARV-based HIV prevention product options as well as those beyond the drug-based modalities. While the specifics around daily pill taking may not translate to a new injectable product, the women's values and preferences (25) should remain consistent as shown in the systematic review. An interesting line of research would be to examine where some of these preferences and values may develop or change over time. In the interim, products and interventions built around them which respond to and support women's desires to maintain their romantic relationships, safeguard against exposures to HIV, and confer and preserve personal health and well-being will have more success in serving the overall needs of women, in particular in high risk situations such as sex work. Additionally, particular attention should be paid to community education, or at least addressing, rumours which may arise regarding the efficacy or lack thereof of new products as they become available. Potentially the most damaging aspect of new intervention introduction is the lack of accurate awareness and disbelief in the existence and efficacy of a product, which is a core tenant of Normalization theory (26). If the community at large has doubts in an intervention, which could be particularly the case in relation to pharmaceuticals which enter the body and

can have potentially (perceived) lasting, unpredictable effects, then gaining any momentum in uptake beyond the innovators and early adopters who sit in the front of the Diffusion of Innovations curve will be slow and potentially impossible (27).

7.4. Recommendations for policy and practice

PrEP represents a game-changer in HIV prevention, but must be implemented with consideration for how it will be integrated into people's lives. It is important for policy makers and implementers to take into account the vast body of knowledge already produced from the past 20 years in research and development of new HIV prevention options, as well as the emerging data on PrEP use as the early stages of delivery unfold. It is easy to focus on the 'low-hanging fruit' regarding the practicalities of implementation – where PrEP should be delivered in terms of clinics, who should deliver it in terms of practitioners, and initial messaging about its availability. However, none of this will make a difference in successful implementation if there is wide-spread disbelief in the existence or efficacy of PrEP, or it is stigmatised as a "sex worker pill", for instance. Social normalization will need to play a key role in PrEP programming if there is to be any measurable success in reaching those who need it most. This will require early and constant engagement with communities until a 'tipping-point' of understanding, or saturation of education, is reached. In addition, the PrEP intervention will need to be situated appropriately in terms of applicability within the contexts of potential users' realities for it to be assimilated. If all of these facets of implementation are carefully considered, PrEP may also help to strengthen existing services as it provides multiple opportunities for refreshing HIV prevention training of health care staff as well as a new incentive for people in communities to seek care and explore their HIV prevention options.

As shown in this research, the differences between sex worker contexts can be vast, and therefore a certain amount of formative exploration before implementation is merited. This is suggested as a best practice before introducing oral PrEP, or any other new intervention, into standard of care in clinics. In addition, including community members in every step of the process to develop and rollout PrEP interventions will be critical. Participatory research has been advocated, particularly in the HIV/AIDS field, but UNAIDS and AVAC who developed a guidance document called Good Participatory Practice (GPP) (28) which mirrors Good Clinical Practice (GCP) as an essential research standard. Throughout this PhD research and the larger TAPS project, sex workers were engaged in design and decision-making, which helped bolster the credibility of the research overall.

Continuing along the theme of inclusion, it will be important to involve, or at least allow for the involvement of partners in PrEP uptake and use. While the research presented here from the TAPS study illustrated that most women would take PrEP with or without their partner's involvement, the research presented as part of the systematic review and in part from TAPS shows that partners will influence decision-making. Not all women will be empowered to take-up and use PrEP, and those women are potentially at even higher risk if they are in a position of disempowerment. Programming for PrEP will need to allow for the maintenance, and potentially even strengthening of relationships which should have the added benefit of social support for PrEP use.

7.5. Final Thoughts and Reflections

This research spanned a number of phases, methods, contexts, and regularly interacted with policy and normative guidance development at local, national, and international levels. These were exciting and satisfying aspects of this PhD endeavour, but also challenging alongside the management and leadership of the TAPS project where there were high expectations of quality and rapid outputs. Nevertheless, this was a learning experience of a lifetime.

Implementation research is never straightforward, and part of undertaking it is expecting the unexpected. Almost all of the aspects of the entire process, from design to analysis, were filled with unpredictable turns of events, however these were also important learning opportunities. Navigating regulatory hurdles, political relationships, and becoming accepted and a trusted friend of the local community brought many challenges and rewards. Perhaps the most rewarding on a personal level was having the opportunity to build capacity of staff from long-time public health nurses with more than 20 years of experience in the public sector but no previous experience in research, to sex worker peer educators who had never had the opportunity to give presentations or lead their own areas of research-based work (such as study recruitment). This was a personal source of daily joy to see team member grow in their jobs and build an incredibly productive and solid team, which will be dearly missed now that the work is coming to an end.

One of the interesting aspects of this work not discussed previously in detail in this PhD, or elsewhere, was the process of decision-making around options for the overall research approach which took place even before the demonstration project design and engagement in

South Africa. Early in the discussions about pursuing a demonstration project in the South African FSW context, considerations were discussed among the four primary TAPS investigators as to whether it would be possible (and/or necessary) to conduct the research as a randomized control trial in order to directly evaluate impact. After much debate, several conclusions were reached. First, that it would be unethical not to offer the interventions to a control group as we knew at the time that early ART (or test and treat) would eventually become the standard of care, and most likely during the course of the study. The PROUD study is an example of where the study ended up being unblinded when the PrEP intervention was shown to be so effective it was no longer ethical to withhold it (29). While we did not know at the time that this would be the case for PROUD, we did strongly suspect an RCT would be difficult to pursue from start to finish with no significant deviations which would make it unnecessarily complex. Second, there were not enough concentrated FSW populations in areas where we could operate and sufficiently randomize to account for heterogeneity. This was also considered in relation to potentially incorporating randomized, nested adherence interventions such as using a medication event monitoring system (MEMs) bottle caps (30) to more objectively look at adherence in addition to drug level analyses, however statistically it was not going to be possible given estimated sample sizes and the desire to only evaluate intervention components which could then be incorporated in a national rollout. The drug level analyses were justified as they did not require a large amount of blood and that could be drawn at the same time as standard monitoring (for creatinine) without disruption to participants. Third, was the limited funding for the TAPS study, which was supported through a number of channels, starting primarily with the Bill and Melinda Gates Foundation grant, then supplemented by USAID funding with donations from Gilead and Mylan of study drug and other in-kind support from partner projects within Wits RHI.

These considerations are what led to the choice of a relatively straight forward implementation study with as few obvious research components as possible to avoid the participant experience becoming to akin to research and less real-world. In terms of the internal and external validity related to efficacy and effectiveness research, as discussed by Singal et al (31), demonstration projects fall at the far end of the effectiveness side of the continuum. This means, that in the end, this research had to live with a certain level of uncertainty around validity in the quantitative findings, especially with a reduced sample size and no comparison group. However, the point was always to practically answer the programmatic aspects (including applicability and acceptability) of delivering PrEP to FSWs in

clinics servicing urban sex work environments. The research presented here provides a large piece of that story.

7.6. Conclusions

This body of PhD research has illustrated the personal, social, and environmental nuances within which oral PrEP as an HIV prevention product for FSWs is taken up and used in urban settings in South Africa. The applicability of PrEP for FSWs is dependent upon their sex work contexts and the ways in which PrEP is made accessible in tailored delivery. Acceptability is a nuanced dynamic influenced by situating the need for PrEP within the complexities of FSW's personal risks and responsibilities, reconciling trust and belief in the product, developing habits for ease of use, and navigating relationships. Through the research in-country, the thematic constructs explored in the systematic review were tested in practice and developed in more depth, where relationship dynamics, trust in partners and social circles as well as oral PrEP itself played a significant role in decision-making around uptake and use. Sexual satisfaction was not as central a component in this work, but empowerment and control in having the ability to maintain personal safety at work and in romantic relationships was still very central.

The MSEM framework, linked with principles of Implementation Science, was useful in situating the research questions and findings in an organised and easily translatable format for providing evidence to further the rollout of oral PrEP in South Africa and beyond. Key demographic and behavioural characteristics of women who took up PrEP signal an accurate perspective of self-assessed risk, driven by the realities of sex work and personal responsibilities to support families, which were further illuminated through in-depth individual discussions with participants. The holistic nature in which this research was undertaken represented a large managerial undertaking with multiple, simultaneous processes and learning pathways which led to important findings around the diversity of sex work markets and the fluidity of social-contextual interactions which ultimately interact with the effectiveness of oral PrEP use. Successful policy and practice should take these complexities into account when developing and scaling-up oral PrEP interventions for FSWs. While the specifics of these complexities may not necessarily apply to all contexts and other populations, many lines of inquiry around motivations and barriers to use will be universal.

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8.0 List of Appendices

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Appendix i. LEO Ethics Letter

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

LSHTM

23 June 2015 23 June 2015

Dear ,

Study Title: TAPS Demonstration Project - PhD Research

LSHTM ethics ref: 9645

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	PrEP Demo Project_IDI Guide v1_14 May 2014_FINAL	14/05/2014	v1
Protocol / Proposal	Protocol_PrEP and ImmediateTreatment for FSW_v27_v2_date 5 August_CLEAN FINAL 2	05/08/2014	v2
Local Approval	MCC Approval_15 Oct 2014	15/10/2014	1
Protocol / Proposal	TAPS Demographic and Behaviour Questionnaire_Jan 2015	12/01/2015	v3
Local Approval	HREC Approval of CRFs and Study Materials	29/01/2015	3
Local Approval	MCC Amendment Approval 17_Feb 2015	17/02/2015	2
Information Sheet	ICF_PrEP Intervention_dated_01Apr2015_v2_English_CorrectFooter_1 April 2015	01/04/2015	2
Information Sheet	ICF_Qualitative Participant IDI_dated_01Apr2015_v2_English_CorrectFooter_1 April 2015	01/04/2015	2
Local Approval	HREC Approval of changes to ICFs	16/04/2015	2
Investigator CV	R Eakle_Professional CV_2015	06/05/2015	1
Local Approval	Wits HREC Approval 11 Sept 2014	11/09/2015	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

(b) The Council shall be notified of any decision to discontinue the Clinical Trial. The reason for such cancellation shal be stated.

(c) The Clinical Trial shall be conducted in accordance with the Protocol submitted to the Council. Any Amendment/(s) to the Protocol shall first be submitted to the Council for approval. All Clinical Trials be conducted in accordance with ICH GCP Guidelines, and the South African Clinical Trials Guidelines.

(d) The medicine shall be administered by or under the direction of the authorised Trialist. In the case where the Trialist permits another Medical Practitioner to administer a medicine, which is exempted from the registration for the purpose of the Trial, the Trialist shall remain responsible for any eventuality arising from such usage.

(e) Where a Trialist who is not authorised in the initial Authorisation, is requested to participate in the Clinical Trial, the Council requests that the relevant MCC Curriculum Vitae Format be completed detailing their Full Names, Address and Qualifications of the proposed Trialist (Practitioner) concerned, and be submitted to the Council for Approval.

(f) In the event of the authorised Trialist ceasing to participate in the Clinical Trial, the Council shall be informed and the reason for such cessation shall be given.

5. **PROGRESS REPORTS**

The Council must be furnished with signed six-monthly Progress Report from each Trialist including a report of the Final Results.

6. **INFORMED CONSENT**

It is a Council requirement that in all Clinical Trials the 'Principles of Informed Consent' should be adhered to. This applies to Trial Volunteers, as well as Participants (Patients). (Reference: Section 4.8 of ICH GCP Guidelines and Section 3.5 of SACT Guidelines).

Yours faithfully

[redacted]

MRS MOLEBOGENG RAMATHE

FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

MCC TRIAL REFERENCE NO: 20140740

Appendix ii. HREC FGD Ethics Letter

R14/49 Professor Helen Rees

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131009

NAME: (Principal Investigator)	Professor Helen Rees
DEPARTMENT:	Wits Reproductiver Health & HIV Institute Hillbrow Health Precinct
PROJECT TITLE:	Focus Groups for the Sex Worker ART for Prevention (SWAP) Project: Assessing the Acceptability and Feasibility of a Comprehensive Prevention, Treatment and Care Programme Tailored for Female Sex Workers, Including New and Current HIV Prevention Technologies as well as ...
DATE CONSIDERED:	25/10/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	[redacted]
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/01/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix iii. LEO FGD Ethics Letter

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Ms. Robyn Eakle

LSHTM

3 July 2015

Dear Applicant Title Eakle

Submission Title: Preparing for PrEP - Focus Groups with FSWs

LSHTM Ethics Ref: 10102

Thank you for responding to the Observational Committee Chair's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	HREC FGD Original Application	03/10/2013	1
Covering Letter	Response to LEO Feedback_signed_June 2015.docx	25/06/2015	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DA Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Page 1 of 1

Appendix iv. TAPS HREC Letter

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

08 September 2014 **FAXED & COURIERED**

Ms R Eakle

Wits Reproductive Health and HIV Institute (Wits
Hugh Solomon Building
22 Esselen Street
Hillbrow, Johannesburg
2001

Fax: 086 407 1937

Dear Ms Eakle,

PROTOCOL: WRHI046 - THE TAPS DEMONSTRATION PROJECT. EXPANDED USE OF ART FOR TREATMENT AND PREVENTION FOR FEMALE SEX WORKERS IN SOUTH AFRICA

ETHICS REFERENCE NO: 140502

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial was reviewed by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol Review Committee (PRC) on: 30 May 2014.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC-001 and SOP-IEC-005, Item 3.4).
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

8.2 Protocol Review Committee Approval Signature page signed by the Acting Chairperson of the PRC.

8.3 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* MCC Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.
* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).
* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

Prof Woodiwiss approves this study pending receipt of the final questionnaire (in response to query 7 the investigators state that they will provide the Wits HREC with the final questionnaire which is still being amended in order to shorten it) before the study commences.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,

[redacted]

PROF PETER CLEATON-JONES
For and on behalf of the Human Research Ethics Committee: (Medical)

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

Ethics Reference No.	140502	Date of Meeting	30 May 2014
		Recertification Due	29 May 2015 (If applicable)
Principal Investigators:	Prof Helen Rees	Investigators:	Ms RG Eakle
			Dr GB Gomez
			Prof WDF Venter

Protocol Title:	The TAPS Demonstration Project. Expanded use of ART for Treatment And Prevention for female Sex workers in South Africa

	DOCUMENTS REVIEWED	Tick As Appropriate:		Yes	No
Protocol Number	WRHI046	Date:	05 August 2014		
Protocol	Study Protocol v.2 - The TAPS Demonstration Project - WRHI046	Date:	05 August 2014	☑	☐
	Study Protocol v1 - The TAPS Demonstration Project - WRHI046 - WITHDRAWN	Date:	14 May 2014	☑	☐
	Study Protocol v.1 - The TAPS Study - WRHI046 - WITHDRAWN	Date:	06 May 2014	☑	☐
Investigator's Brochure	Package Insert: ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) - Version: October 2013 - Dated:			☑	☐
	Package Insert: TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) - Version: October 2013 - Dated:			☑	☐
Subject Information/Consent Form	Participant Costing Study Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	SMS Messaging Service Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Provider Costing Study Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Storage of Blood Samples for Future Use Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Provider Group Discussions Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Participant Qualitative Study Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Immediate Treatment Screening and Enrolment Participant Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Pre-Exposure Prophylaxis (PrEP) Intervention Screening and Enrolment Information Sheet and Informed Consent Form - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Example of Communications Materials (These will be available in English, Sesotho and IsiZulu) - Version: - - Dated:			☑	☐
	Short Message Service (SMS) Messages for Sex-worker Demo Project Protocol - Version: - - Dated:			☑	☐
Advertisements					
Questionnaires	Participant Case Report Form (CRF): Exit Study Visit Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Pharmacist Adherence Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Regular Study Visit Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Enrolment Demographics and Behaviour Questionnaire - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Initial visit form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Eligibility Checklist - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Eligibility - Participant Information and Demographic Screening Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Eligibility - Clinical Screening Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	Participant Case Report Form (CRF): Decline Study Participation Form - Version: v.1 - Dated: 14/May/2014			☑	☐
	TAPS Assessment of Understanding - Version: 2.0 - Dated: 05/Aug/2014			☑	☐
	Provider Group Discussion Guide - Version: - - Dated:			☑	☐
	Patient-related costs: Information sheet and informed consent for PrEP or immediate treatment participants - Version: - - Dated:			☑	☐
	Healthcare-related costs: interview guide for healthcare professionals - Version: - - Dated:			☑	☐
	Healthcare-related costs: data requirements - Version: - - Dated:			☑	☐

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

	In-depth Interview Guide - Version: Draft/Version 1 - Dated:		☑	☐
Insurance/Compensation	TriHead Financial Services cc - No Fault Clinical Trial Insurance - Reference No: TAPS/TRUVADA-MAY 2014	Valid From 01 Aug 2014 To: 31 Dec 2016	☑	☐
Synopsis of Study/Trial Summary	Treatment And Prevention for Female Sex Workers		☑	☐
Other Documentation	NHREC Trial Application ID: 3740 - Dated: 24/Apr/2014		☑	☐
	Protocol Synopsis - The TAPS Demonstration Project - Dated: 06/May/2014		☑	☐
	PRC Application Form - Dated: 08/May/2014		☑	☐
	HREC Application Form - Dated: 08/May/2014		☑	☐
Relevant Trial Hospital/(s)	Wits RHI - Reproductive Health & HIV Institute (Esselen Str)		☑	☐
	London School of Hygiene and Tropical Medicine (LSHTM)		☑	☐
Syndicate and/or Research Unit	Wits RHI - Reproductive Health & HIV Institute (Esselen Str)		☑	☐
	London School of Hygiene and Tropical Medicine		☑	☐

DETAILS OF COMMITTEE	
Name	University of the Witwatersrand Human Research Ethics Committee: (Medical)
Address	Research Office, Senate House University of the Witwatersrand, 1 Jan Smuts Avenue, BRAAMFONTEIN, Johannesburg, 2000

DETAILS OF MEETING	Yes	No
Is the investigator a member of the committee ?	☐	☑
If "Yes" did he/she vote ?	☐	☑
Is the Committee organised and operated according to applicable laws and regulations together with ?	☑	☐
Local GCP requirements ?	☑	☐
ICH GCP requirements ?	☑	☐
FDA GCP requirements ? FWA Registered No. IRB00001223	☑	☐
Progress reports required either in March and September or six monthly from start of study ?	☑	☐

DECISION ON APPROVAL : Is approval given to conduct the trial ?	Tick As Appropriate
Yes - with no conditions	☐
Yes - with conditions	☑
Specify conditions : APPROVED WITH CONDITION: Prof Woodiwiss approves this study pending receipt of the final questionnaire (in response to query 7 the investigators state that they will provide the Wits HREC with the final questionnaire which is still being amended in order to shorten it) before the study commences.	
No	☐
Specify reasons	

SIGNATURES		
I confirm that the details on this form are correct:		Date
Name: **Prof PE Cleaton-Jones** Chair / Deputy Chair of Committee	Signature: [redacted]	08 September 2014

DECLARATION OF INVESTIGATOR/(S)

To be completed and ONE COPY returned to the Secretariat for the HREC at Wits Health Consortium, 8 Blackwood Avenue, Parktown, 2193 or Fax To: 011 274-9281

I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with these conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution, I/we will communicate with the Chairman of the Human Research Ethics Committee: (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthorised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures.

Any approval given by the HREC is conditional upon consent being obtained by the investigator/s from the Superintendent (or equivalent official) of the Hospital, Clinic or Institution in which the research is, in part or full, to take place.

The Chairman may of course at his discretion place the matter before the full Committee.

DATE:_____ SIGNATURE:_____ NAME:_____

PROTOCOL NUMBER **WRHI046** ETHICS REF.: **140502**

Date Printe 09 September 2014

WITS HEALTH CONSORTIUM (Pty) Ltd.
Reg No.: 97/13443/07

Wits Clinical Research

8 Blackwood Avenue, Parktown, 2193, South Africa
Tel. +27-11-274-9200. Fax: +27-11-274-9261
Postnet Suite 189, Private Bag x2600, Houghton, 2041

FAXED & COURIE

Prof Helen Rees,

Wits Reproductive Health & HIV Institute
Hillbrow Health Precinct, Hugh Solomon Building
22 Esselen Street (Cnr Klein Street)
Hillbrow
2001

Fax: 086 639 4306

Dear Prof Rees,

PROTOCOL NO: WRHI046

PROTOCOL TITLE: The TAPS Demonstration Project. Expanded use of ART for Treatment And Prevention for female Sex workers in South Africa

PRC REFERENCE NUMBER: 140502

Please be advised that your trial application was:

APPROVED

The Expert Reviewer /(s): Dr FM Conradie

Also reviewed by: Mrs J Palmer: Acting Chairperson Protocol Review Committee
Dr NM Mazamisa: Gauteng Department of Health

Yours sincerely

[redacted]

Acting **MRS JENNIFER PALMER**
Chairperson: Protocol Review Committee
08 September 2014

cc.
WRHI Wits Reproductive Healt Ms R Eakle

Tel 011 368 5350 Cell 076 671 9859 Fax 086 407 1937

HUMAN RESEARCH ETHICS COMMITTEE MEMBERS: (MEDICAL)
UNIVERSITY OF THE WITWATERSRAND

Attendance Register for the Ethics Meeting held on 30 May 2014 from 12:30 - 15:00

Venue: EXECUTIVE COMMITTEE ROOM, Ground Floor, Phillip V Tobias Building, Cnr York Road & 29 Princess of Wales Terrace

AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Adam	Y	Dr	Obstetrics & Gynaecology	MB BCh; FCOG	F	Absent
Cleaton-Jones	PE	Prof	Biomedical Ethics	BDS; MB BCh; PhD; DA (SA); DTM&H; DSc (Dent), FCD (SA) DPH; PhD Hon Causa, MASSAfr	M	Present
Conradie	FM	Dr	Infectious Diseases/HIV/TB	MB BCh; DTM&H; MSc; Dip HIV Man	F	Present
Cooper	PA	Prof	Paediatrics	MB BCh, PhD, DCH (SA), FCPaeds (SA)	M	Absent
Cubasch	H	Dr	Surgery	FCS (SA)	M	Absent
Dessein	PHMC	Prof	Rheumatology	MD, FCP (SA), FRCP, PhD	M	Present
Dhai	A	Prof	Biomedical Ethics	MB ChB; FCOG; LLM; PGDipIntResEthics	F	Absent
Donde	B	Prof	Radiation Oncology	MB BCh, MMed Rad (T)	M	Present
Etheredge	H	Ms	Biomedical Ethics	MSc Med, BA	F	Present
Feldman	C	Prof	Pulmonology	MB BCh, PhD, DSc, FCP (SA), FRCP	M	Present
Gerrand	P	Ms	Social Work	MA (Social Work)	F	Absent
Langley	G	Prof	Nursing	MSc (Nursing), PhD, MPhil (Ethics)	F	Absent
Lownie	MA	Prof	Maxillo-Facial & Oral Surgery	BDS, BA (Hons), DipMFOS, FCMFOS(SA), MEd	F	Present
Naidoo	Shan	Prof	Public Health	MB BCh, DMTH, DHSM, DOH, MMED	M	Absent
Naran	NH	Dr	Chemical Pathology	PhD	M	Present
Paruk	F	Prof	Anaesthesia	MB ChB, FCOG(SA), Crit Care(SA), PhD	F	Absent
Penn	C	Prof	Speech Pathology	BA (Sp&HTh), PhD, CCC SL-P, OMS	F	Absent
Penny	C	Dr	Internal Medicine	BSc Hons, PhD	M	Present
Ross	M	Prof	Public Health	MB ChB, FFCH(SA), MFamMed, MFPH	F	Absent
Sanne	IM	Prof	Infectious Diseases/HIV/TB	MB BCh, FCP (SA), DTM&H; MMed & PhD	M	Present
Smith, Cora	C	Prof	Psychiatry	BA, BA (Hons), M.A (Clin.Psych), PhD	F	Present
Stewart	A	Prof	Physiotherapy	BSc (Physio), MSc, PhD, DPE	F	Present
Szabo	CP	Prof	Psychiatry	MB BCh, MMed, MScMed, PhD; FCPsych(SA)	M	Absent
Thom	RGM	Prof	Psychiatry	MB ChB, DCH, FCPsych, PhD	F	Absent
Tsotsi	NM	Dr		BDS; MPH; MSc Med; PGDipInt ResEthics	F	Absent
Van Gelderen	CJ	Prof	Obstetrics & Gynaecology	MB BCh, FRCOG, FCOG(SA)	M	Present
Velaphi	S	Prof	Paediatrics	MB BCh, FCPaeds, MMed	M	Absent
Vorster	M	Prof	Psychiatry	BA, MB BCh; MMed, FCPsych(SA), PhD PGDipIntResEthics	F	Present
Willem	P	Dr	Human Genetics	MD, PhD	F	Present
Woodiwiss	AJ	Prof	Cardiovascular Pathophysiology	BSc Physiotherapy, BSc, MSc, PhD	F	Present

NOT AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Egan	A	Father	Theology	BA (Hons), MA, MDiv, STL, PhD	M	Absent
Guidozzi	Y	Adv	Lawyer	BSc (Nurs), LLB, MBA	F	Absent
Ikalafeng	B	Dr	Governance	BSc (Hons), MSc, PhD	F	Absent
Myburgh	C	Prof	Educationist	BSc (Hons), MCom, DEd, HED	M	Present

Peter Poggenpoel	JR M	Adv Prof	Lawyer Psychiatric Nursing	BCom; LLB; LLM RN; PhD	M F	Absent Present

RETIRED MEMBER OCCASIONALLY CO-OPTED FOR SURGICAL OPINION ON A PROJECT

Oettle	GJ	Prof	Surgery	BSc (Hons), MB BCh, FRCS	M

Note 1: This committee has been in continuous operation since October 1966
Note 2: The large committee size is to ensure a good attendance at meetings - size 23 core and 14 alternate members
Note 3: A Quorum is 14 members according to the 60% required by SA National Guidelines (ref 2 below)

This is to certify that the Human Research Ethics Committee: (Medical) of the University of the Witwatersrand operates according to the following guidelines of good clinical practice:

1. **ICH Harmonised Tripartite Guideline for Good Clinical Practice.**
2. **SA National Department of Health 2006 Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006).**
3. **Declaration of Helsinki 2013.**

The Committee's United States Federal Wide Assurance details are:

1. **Country code 3F.**
2. **FWA Number: FWA00000715.**
3. **University of the Witwatersrand: IORG0000862.**
4. **Human Research Ethics Committee: (Medical): IRB00001223.**

[redacted]

Appendix v. TAPS MCC Letter

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

CC:0866347576

MEDICINES CONTROL COUNCIL
The Registrar of Medicines, Private Bag X828, PRETORIA, 0001
Tel 012 395 9000 Fax 012 395 9201
Tel: *Enquiries:*
Fax: *Reference:*

FAX AND MAIL TO

MRS MOLEBOGENG RAMATHE

N2/19/0/2 ()

Ms R Eakle

Datum * Date **15 October 2014**

Wits Reproductive Health and HIV Institute
Hugh Solomon Building,22 Esselen Street
Hillbrow
JHB
2038

Tel: 012 395 8128
Fax: 012 395 8775

Fax: 0864071937

Dear Ms Eakle,

AUTHORISATION FOR THE IMPORTATION OF UNREGISTERED MEDICINE IN TERMS OF SECTION 21 OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965)

PRODUCT: TRUVADA & COMBINATION TDF + FTC+EFV(ATRIPLA)

Your application letter dated **16 May 2014** refers

1. **RESOLUTION AND APPROVAL**
It was recently resolved by the Medicines Control Council that; the clinical trial application according to the following Protocol be approved :-
WRHI046 protocol version 1.0 dated 14-May-14
Expanded use of ART for treatment and prevention for female Sex workers in South Africa

1.1 **BEFORE COMMENCEMENT OF TRIAL**
Please Note: Copies of written Ethics Committee approval/(s) to be submitted to MCC before the study commences.

2. **AUTHORISATION**
Authorisation is hereby granted for the importation and administration of a sufficient quantity, for the duration of the trial, of the unregistered medicine:
TRUVADA & COMBINATION TDF + FTC+EFV(ATRIPLA)
solely for the purpose of a clinical trial to be conducted by:

Prof H Rees	WITS Reproductive Health and HIV Institute	Principal
Prof WDF Venter	WITS Reproductive Health and HIV Institute	

3. **PLEASE FORWARD**
It is a requirement that a copy of this letter be forwarded to all the relevant Triallist/(s), including the approving Ethics Committee(s).

4. **THIS AUTHORISATION IS SUBJECT TO THE FOLLOWING PROVISOS:**
(a) The Council shall be informed immediately of any toxic effects or death, which may occur during the Clinical Trial and of any data received which, might cast doubt on the validity of the continuation of the Clinical Trial.

(b) The Council shall be notified of any decision to discontinue the Clinical Trial. The reason for such cancellation shal be stated.

(c) The Clinical Trial shall be conducted in accordance with the Protocol submitted to the Council. Any Amendment/(s) to the Protocol shall first be submitted to the Council for approval. All Clinical Trials be conducted in accordance with ICH GCP Guidelines, and the South African Clinical Trials Guidelines.

(d) The medicine shall be administered by or under the direction of the authorised Trialist. In the case where the Trialist permits another Medical Practitioner to administer a medicine, which is exempted from the registration for the purpose of the Trial, the Trialist shall remain responsible for any eventuality arising from such usage.

(e) Where a Trialist who is not authorised in the initial Authorisation, is requested to participate in the Clinical Trial, the Council requests that the relevant MCC Curriculum Vitae Format be completed detailing their Full Names, Address and Qualifications of the proposed Trialist (Practitioner) concerned, and be submitted to the Council for Approval.

(f) In the event of the authorised Trialist ceasing to participate in the Clinical Trial, the Council shall be informed and the reason for such cessation shall be given.

5. **PROGRESS REPORTS**

The Council must be furnished with signed six-monthly Progress Report from each Trialist including a report of the Final Results.

6. **INFORMED CONSENT**

It is a Council requirement that in all Clinical Trials the 'Principles of Informed Consent' should be adhered to. This applies to Trial Volunteers, as well as Participants (Patients). (Reference: Section 4.8 of ICH GCP Guidelines and Section 3.5 of SACT Guidelines).

Yours faithfully,

[redacted]

MRS MOLEBOGENG RAMATHE

FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

MCC TRIAL REFERENCE NO: 20140740

Appendix vi. R Eakle GCP Certificate

GOOD CLINICAL PRACTICE
Basic Course

Ms RG Eakle

successfully completed the course on

27 & 28 March 2014

Venue: Wits Health Consortium, 8 Blackwood Ave, PARKTOWN
Presented by: Bridget Minnie

[redacted]

GENERAL MANAGER –TRAINING

Date of issue: 1 April 2014 – valid for 3 years

[redacted]

TRAINING COORDINATOR

Contact: 011 274 9200 or mmaddocks@witshealth.co.za

COURSE CONTENT:
Drug Development Process
Historical Review of GCP
South African GCP
Regulatory process in South Africa
Study Documents
Patient Recruitment and Retention
Informed Consent
Investigational Product
Safety Reporting
Responsibility of the Study Team
Standard Operating Procedures
Laboratory Issues
Monitoring
Audits

A wholly owned subsidiary of the University of the Witwatersrand

SACRA GCP Registration No:
SACRA/GCP/97/2014

The Health Professions Council of South Africa approved CPD reference is as follows:
Accreditation No:
MD808/083/01/2014
Activity No.: 32556
Category: 1B
Points: 11

MD808/084/01/2014
Activity No.: 32557
Category: 2L
Points: 4 Ethics

GOOD CLINICAL PRACTICE

Refresher

Ms R Eakle

attended the course on

Date: 23 May 2017

Venue: BEESA Conference Centre, 5 Sherborne Rd, PARKTOWN

Facilitator: Lesley Burgess

The Health Professions Council of South Africa approved CPD reference is as follows:

MDB08/007/01/2017 Activity No: 35660 Category: 1B Points: 2
MDB08/004/01/2017 Activity No: 35659 Category: 2L Points: 4 Ethics

This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors

COURSE CONTENT:

ICH Guideline for Good Clinical Practice - E6(R2) 9 November 2016
SA Good Clinical Practice Guidelines – 2nd Edition 2006
Historical Overview of GCP
GCP Audits and Inspections
Research involving Genetic Studies
Litigation in Clinical Trials
Topical Issues in Clinical Research

academic advance
A division of Wits Health Consortium (Pty) Ltd

[redacted] [redacted]

GENERAL MANAGER – TRAINING TRAINING COORDINATOR

Date of Issue: 23 May 2017 – valid for 3 years
Contact: 011 274 9200 or training@academicadvance.co.za

Appendix vii. Focus group participant information sheet and consent form

PROJECT INFORMATION SHEET AND INFORMED CONSENT

PROJECT TITLE: Focus Groups for the Sex Worker ART for Prevention Project: Assessing the acceptability and feasibility of a comprehensive prevention, treatment and care programme tailored for female sex workers, including new and current HIV prevention technologies as well as the test and treat approach to treatment and care.

This consent form is for participants who agree to participate in a focus group interview as part of a research project. The following statement is to be read to the participant.

PROJECT INFORMATION

My name is _____. I am working with Wits RHI the organization supporting the project to assess the acceptability of comprehensive prevention, treatment and care services for female sex workers (FSW).

I would like to talk to you about participating in a focus group study to better understand what you think about the current health services you receive and whether there are additional services you would like access to. This information will help us understand whether there is an opportunity to provide new services along with existing ones.

We are asking you to participate in a focus group discussion to help us understand your opinion about these proposed services and if you feel they make sense for your needs. We would like to ask you questions regarding your experiences of health services in general, if you have experienced any difficulties in accessing care and, if so, what those were. We would also like to know about your opinions of new potential options for HIV prevention and treatment.

A focus group is a formal group discussion. We are asking groups of up to 10 women to join us for an hour and a half. If you feel uncomfortable with any of the questions asked, you can chose not to answer them without any consequences. You can also stop your participation at any time, without any consequence. If you decide not to participate in the focus group discussion this will not affect the services you receive from the clinic.

During the focus group discussion, we will provide drinks and snacks.

We have been sponsored by the AIDS Fonds Netherlands to conduct these focus groups.

REIMBURSEMENT

You will be reimbursed as a participant in this study for travel expenses at R50.

CONFIDENTIALITY

Efforts will be made to keep your information confidential through the use of participant identification numbers or fake names. We will ask participants to maintain confidentiality however there is no way to ensure this will be respected. We will be audio-recording the focus group discussions, and you may choose to use a different name during the discussions.

However, it is not possible to guarantee confidentiality. In addition, your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- Wits Human Research Ethics Committee, University of the Witwatersrand, an Ethics Committee is a committee that watches over the safety and rights of research participants
- Study staff

In giving consent to participate in these interviews, you will be consenting for these people to review the study data. These records will be utilised by them only in connection with carrying out their obligations relating to this study.

The researchers will do everything they can to protect your privacy. All information will be securely stored under lock and key for two years after publications of results or six years if there are no publications, after which time the information will be destroyed.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

Voluntary:

- Your participation in this focus group is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to other medical care.
- You must inform the study team if you wish to stop participation in the focus group as soon as possible.

ETHICAL APPROVAL OF THIS STUDY

This focus group study has been submitted to the University of The Witwatersrand, Human Research Ethics Committee and written approval has been granted by the committee.

PARTICIPANT QUESTIONS

Do you as the participant have any questions?
YES / NO (Please list if yes)

_____
_____
_____
_____
_____
_____

INFORMED CONSENT

I hereby consent to participate in a focus group discussion to help assess the acceptability of a comprehensive HIV prevention, treatment and care service programme tailored for female sex workers. By signing this form, I acknowledge the following:

- I have read (or have had read to me) and understood the project information statement.
- I understand that the focus group is for the purposes of this research project only.
- I am aware that the results of the study, including personal details will be anonymously processed into a study report.
- Participation is voluntary and that I can withdraw at any time and for any reason. However, I understand that my contribution to the focus group discussions will, by the nature of the focus group, be known to the members of the group.
- The focus group will be conducted at Wits RHI, in Hillbrow.
- I will participate in a focus group of up to 10 people, conducted by two members of the research team and this will take approximately an hour and a half.
- The research team members will periodically ask me to confirm during the discussions that my statements have been accurately understood and interpreted.
- The focus group will be audiotaped and the tapes will be stored separately from this consent form.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the focus group discussions.
- These arrangements have been approved by the Human Research Ethics Committee of the University of the Witwatersrand in South Africa.

Focus Group Consent:

☐	Yes, I agree to participate in this focus group

☐	No, I do not want to participate in this focus group

Audio recording consent:

☐	I agree to the audio recording of this focus group

☐	I do not agree to the audio recording of this focus group

Signature of volunteer:

Signature/mark or thumbprint		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	:		

Signature of witness (if applicable):

Signature/mark or thumbprint		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	:		

Signature of study staff taking consent:

Signature/mark or thumbprint		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	:		

Appendix viii. FGD Discussion Guide

Interviewer _____ Site/Venue: _____Date:_____

INSTRUCTIONS FOR THE INTERVIEWER – How to use this IDI Guide

1. There are 3 levels of questions:

   - Numerical research questions/topic areas highlighted in gray: the questions/areas that we as researchers want to get answers to. These don't need to be read aloud.

   - Discussion questions: the questions that you as the Interviewer will ask respondents in order to get answers to the research questions. **These questions will be underlined and in bold.**

   - Probes: they are indicated with a bullet. The interviewer should ensure that key topics listed in the probes have been addressed/discussed during the interview. So, depending on what has already been discussed, and the IDI context, you may ask these probes or not.

2. *Instructions/suggestions to interviewer are in italics and brackets [ ].*

3. The discussion guide is divided into three columns.

   - **The left-hand column** contains the research questions, discussion questions and probes. The discussion questions are suggestions for getting the discussion going. It is not required to read them verbatim, but they are written to ensure some consistency across discussion. You may adapt the question, depending on how the discussion develops, and you as the Interviewer will have to ensure that at the end the research questions have been answered.

   - **The right-hand column** is for summarising the themes brought up by the women in the discussions. These should be summaries of the general issues raised in connection with the research question. These summaries should be more than just yes/no, but not longer than a few sentences of bullet points. They do not need to be detailed, as we have the details on the tape. **Note: the summaries and yes/no answers should be filled by the Interviewer immediately after the FGD.**

INTRODUCTION

Welcome the participants and thank them for coming.

Explain the general purpose of the discussion:
"We are holding a few discussions with up to 10 women at a time to talk about experiences with health care in general and more specifically HIV testing, prevention and care services. These discussions will help us understand whether we can put together a set of services tailored especially for female sex workers that will support their needs. We would like to find out what you think about current services, what is missing from them, what kinds of services you wish were available, difficulties in accessing testing and care, and your thoughts about new potential services."

Introduce the team and the different roles of the members.

Outline general ground rules such as the importance of everyone speaking up, talking one at a time, and being prepared for the moderator to interrupt to assure that all the topics can be covered.

Address the issue of **confidentiality**: Inform the group that information discussed is going to be analysed as a whole and that the participants' names will not be used in any analysis of the discussion.

Explain the presence and purpose of audio recording equipment.

Before starting the discussion, the Interviewer explains to the group (please state verbatim):

We will begin the tape recorder now. [Interviewer: s*tart the tape recorder.]*

As you know from your informed consent, this focus group discussion will be tape recorded today. Please verbally indicate that you are aware that we are tape recording this session and that it is okay with you. [*Interviewer: be sure to get a verbal okay from the group.]*

Have the group members introduce themselves. They should create a nickname for the discussion. Have them write it down on a sheet of paper that they will keep. Ask for any questions.

FOCUS GROUP QUESTIONS

	Research Question, IDI Questions, Probes	Summary/Notes
GENERAL HEALTH SERVICES KNOWLEDGE SECTION		
1.	What are the group's experiences with general health care services? **What sort of experiences have you had getting general healthcare?** • Where do you usually go to get general healthcare? (e.g. location and proximity to home and work, type of facility) • What makes a clinic good? • Are there services you wish you could get but are unable to? • What are some of the services you wish you could get, if any? • What are some things that get in the way of going to the clinic or getting services? (e.g. location of clinics, opening hours, waiting times, staff attitudes, having to pay, etc.) • Why would someone not want to go back to a certain clinic?	
HIV PREVENTION KNOWLEDGE SECTION		

2.	What are the group's knowledge and perceptions about HIV testing? **<u>What are your experiences with HIV testing?</u>** • What do you think is a good reason to get tested for HIV? • What reasons do you most commonly hear from others? • Where is the best place to get tested for HIV? Why? • What do you think could be done to improve and increase HIV testing and care service accessibility for women specifically?	
3.	What does the group know about HIV prevention? **<u>What methods are available to protect yourself from HIV and other diseases?</u>** • Is there anything besides condoms that people use? • What do you think is best?	

4.	What does the group know about prevention for HIV-positives? **<u>If someone is HIV positive, what can they do to protect their partners and/or clients?</u>** • Is there anything besides condoms that people use or do? • What do you think is best?	
5.	Is the group familiar with post-exposure prophylaxis (PEP)? **<u>Have you ever heard of someone taking tablets after they thought they may have been exposed to HIV?</u>** • If you know someone who has used PEP, why did they use it? • What do you think about that option?	

6.	Does the group know anything about new HIV prevention options? **<u>Have you heard about any new ways to protect yourself from HIV?</u>** • If so, what are they?	

PrEP SECTION

Introduce PrEP

If they have heard about PrEP, probe on knowledge (oral PrEP, microbicides – what exactly have they heard and from where?)

If no one knows about PrEP continue with the following:

There is a new HIV prevention method called oral PrEP. It is a pill you can take once a day to prevent getting HIV. It has some side effects and you have to take it every day or it won't work. If someone takes PrEP, they have to get tested regularly to make sure they haven't become HIV-positive. It has been tested in clinical trials, but it is not yet available at the clinic. Some clinics may try offering PrEP to small groups of people to see if they will use it.

7.	How does the group feel about oral PrEP as an HIV prevention option? **<u>What do you think about prep as an option to prevent getting HIV?</u>** • What are the good aspects? • What are the bad aspects?	
8.	What does the group think about regular testing to be able to take PrEP? **<u>Do you think women would be willing to get tested for HIV every 3 months to be able to keep taking PrEP?</u>**	

9.	Does the group think there is an ideal candidate for taking PrEP? **<u>What sort of woman should use PrEP? What sort of woman shouldn't?</u>** • Should someone have certain habits in order to take a pill every day to prevent getting HIV? • Would someone need certain support to take PrEP? • Would someone need to have a certain lifestyle to take PrEP?	
IMMEDIATE TREATMENT SECTION		
10.	What does the group think about having immediate treatment available? What do you think about getting treatment right away when someone finds out that they are HIV positive? • Would people want to start treatment right away? • Why or why not? • What would be a good reason to start right away? • Why do you think it might not be a good idea?	
COMBINED SERVICES		

11.	Does the group think combining HIV prevention and treatment services is a good idea? **<u>What do you think about having a clinic where prevention and treatment options are all in one place especially for women/sex workers, including HIV testing, counselling, PrEP and Immediate treatment?</u>** • Would women/sex workers come to a clinic where all of these things were offered? • Why or why not? • Are there services or features that would make a clinic like this better? • What are some examples of those things?	
ADHERENCE SECTION		

12.	What does the group think about ability to take pills everyday such as in the case of PrEP? **<u>What do you think about taking a tablet every day for a long period of time?</u>** • Do you think it is possible? • What experiences have you had with taking medications everyday over a period of time? (e.g. antibiotics or other medication) • What might get in the way of taking a pill every day? • Is it easier to take a pill every day when you feel sick? • What if you don't feel sick?	

13.	What kind of support does the group think a sex worker/woman would need to be able to take a pill every day? What do you think would help a woman take tablets every day if she decided she wanted to take prep if she were HIV negative, or go on treatment right away if she tested HIV positive? • Are there certain methods or tools that would help? • Would social support help? If so, what type of social support? • Could a woman/ sex worker set up reminders of some kind? • What kinds of reminders? • Would SMS to phones help? • Why or why not? • Any other ways? (e.g. setting up a routine…)	
END DISCUSSION		
14.	**Thank you for participating. Any questions or comments??**	

Appendix ix. TAPS Information sheet and consent form

Participant No: _____

Pre-Exposure Prophylaxis (PrEP) Intervention Screening and Enrolment Information Sheet and Informed Consent Form

Study Title:

The TAPS Demonstration Project: Expanded use of ART for Treatment And Prevention for female Sex workers in South Africa

Study number	WRHI046
Study Sponsor	Wits Reproductive Health and HIV Institute
Principal Investigator	Helen Rees
Co-Investigators	Robyn Eakle, Francois Venter, Gabriela Gomez
Site Address	7 Esselen Street, Hillbrow, 2001
Site contact numbers	0616043097 / 011 358 5424

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

INTRODUCTION

Hello, my name is _____ and I am a member of staff for this research study. We are inviting you to take part in a research study for female sex workers. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is sponsored by the Wits Reproductive Health and HIV Institute (Wits RHI), located in Johannesburg, South Africa.

PURPOSE OF THE STUDY

Recent studies have shown that taking antiretrovirals (ARVs) can reduce the chances of getting HIV in uninfected individuals, and can reduce the chances of transmitting HIV by infected individuals.

HIV uninfected individuals can take an ARV pill every day called Truvada®, which can reduce the chances of getting HIV by about 75 percent. One particular study showed that the participants who took their medication consistently had as high as 90 percent protection from HIV infection. When HIV-uninfected people take medication in this way to prevent getting the HIV virus it is called pre-exposure prophylaxis or PrEP. PrEP has been found to be safe to take, meaning it does not have any significant effects on the health of the person taking it.

Other research found that HIV-infected men and women who took ARVs at higher CD4 counts took longer to develop AIDS and were 96% less likely to pass the virus to their sexual partner. This use of ARVs soon after infection is called Treatment as Prevention (TASP) or Immediate Treatment (IT).

In this study, we would like to learn about how easy or hard it is for women to take medications to prevent and treat HIV. Approximately 700 women over 18 years of age will be enrolled in this study – 400 will be HIV-uninfected women taking PrEP and 300 will be HIV-infected women taking IT.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand what the study is about, and if you agree to participate, you will be asked to sign this consent form or make your mark in front of a witness to confirm that you are willing to participate. We will give you a copy of this form to keep at home. As we read through the form there may be some unfamiliar words, so we ask that you please ask us to explain anything you may not understand.

Before you learn about the study procedures, it is important that you know the following:

- You do not have to join this study if you do not want to, and you will not lose any routine medical care benefits at the clinic.
- If you decide to take part in this study, after your enrolment visit you will be in the study for up to 24 months.

- You are free to leave the study at any time if you want. If you choose to leave at any time, you will not lose any routine medical care benefits at the clinic.
- If you decide not to take part in this study, you can still join other research studies later if they become available and you are eligible.

STUDY APPROACH

As mentioned, this study seeks to learn how easy or hard it is for both HIV-infected and HIV-uninfected women to take medications to prevent and treat HIV. Therefore, there will be two arms of the study: a pre-exposure prophylaxis (PrEP) arm for participants who are HIV-uninfected and an Immediate Treatment (IT) arm for participants who are HIV-infected.

Your HIV test shows that you are HIV-uninfected, and therefore eligible to take part in the Pre-exposure prophylaxis (PrEP) arm of the study. This consent form is therefore focused on the PrEP arm of the study, however it is important for you to still know what will happen for those who are HIV infected and in the IT arm.

Pre-exposure prophylaxis (PrEP) arm

HIV-uninfected participants who are willing and eligible to take part in the study will be offered an antiretroviral (ARV) combination called Truvada®. This is a single pill that is to be taken by participants every day during the study. It is a combination of two medications: 200 mg emtricitabine and 300 mg tenofovir. We call this medication oral PrEP.

This medication was chosen for this study because it can be taken once every day with minimal side effects. Also, recent studies have shown that HIV does not easily become resistant to it, and that it can reduce the risk of getting HIV if exposed. It will be provided by this clinic free of charge during the study. This arm of the study will be called the pre-exposure prophylaxis or PrEP arm.

Immediate Treatment (IT) arm

The other arm of the study is called the Immediate Treatment (IT) arm. Only HIV infected women with a CD4 count higher than the nationally implemented guidelines for South Africa are eligible to join this arm of the study. Eligible participants who are willing to take part in the study will be started on a combination of ARVs, namely tenofovir disoproxyl fumarate (TDF) plus lamivudine /emtricitabine (3TC/FTC) plus efavirenz (EFV). This combination pill of three ARVs is known by the brand name Atripla, which also comes in a generic form.

STUDY PROCEDURES

Screening visit

You will need to read about, discuss, and understand the study before you can agree to participate. If you decide to participate, you must sign or make your mark on this form.

If you are willing to be in the study, during today's visit, several things will happen:

- We will ask for your permission to obtain a blood sample at 9 of your study visits. No more than 30 ml (about 6 teaspoons) will be collected at a time. This blood sample will be used for tests at the clinic and by study researchers to check if you have any medical condition that may need to be monitored during the study, or that may prevent you from being eligible to be in the study.
- You will be offered the option of getting SMS's to remind you of clinic visits and to receive weekly supportive messages. You will be asked to sign a separate consent form to confirm that you agree to receive the SMS messages.
- You will be asked when your last menstrual period was and if you may be pregnant. You can elect to take a urine pregnancy test if you would like to confirm whether you are pregnant.
- You will be requested to provide your contact information, as well as a list of people we may contact if we are unable to contact you for any reason. Please note, if we contact anyone on the list you provide, we will not tell them why we are trying to reach you.

Today's visit will last approximately 2 hours.

Follow up visits

After today's visit, you will have regular follow-up visits to monitor your use of Truvada® and to check your health status. The following activities will take place at your follow-up visits:

- Each month, you will receive enough Truvada® pills to last one month. You should take one pill once every day, by mouth. The study staff will counsel you on methods to not forget to take the pills every day. You will be asked about the pills you took during the previous month and the pharmacy staff will provide you with new bottles with pills to last until the following month.
- You will be asked questions about your health since your last visit, your sexual practices and other behaviours, and your experiences of taking medications for HIV prevention.
- You will be asked about things you have done to avoid HIV infection and any other sexually transmitted infections.
- You will receive medical care or referrals for medical care and other services if you need them.
- You will be asked to update your contact information especially phone numbers and where you live, and if there are any changes to the list of people you had given.
- You will be asked when your last monthly period was, and a urine pregnancy test may be done to check if you are pregnant.
- Blood samples will be collected to check how your body is responding to the medication. No more than 30 ml (about 6 teaspoons) will be collected at a time. If at any time you have an abnormal result, we will contact you to let you know and to schedule a visit to recheck the result and evaluate your health.
- The blood samples collected will also be used to check your HIV status; if your HIV test is negative you can continue to receive Truvada®. If your HIV test is positive during any of the follow-up visits you will not receive any more Truvada®. Instead, we will take an additional sample of your blood for resistance testing and you will be referred for care.

- If you consent, a small portion of the blood collected from you will be stored for future drug level testing. Study staff will take you through a separate informed consent form to confirm that you are willing to have your blood samples stored for future testing.
- In addition to using the blood you give for future drug level and resistance testing, we would like permission to store samples for any possible additional tests that may need to be done. At the moment we cannot provide details of what will be looked at as this is not yet known, but we give assurance that no research will be done on the specimens from Wits Entities without the approval of the Wits Human Research Ethics Committee as well as the applicable Research Ethics Committees (REC) at the analysis sites.

Your follow-up visits will last approximately 30 minutes, but could take up to one hour depending on any concerns or issues you might have and want to discuss. If you have any questions or concerns at any time during the study, you may request to speak with a member of the study staff.

PREGNANCY

If you are pregnant you are not eligible to join in the study.

At each study visit you will receive counselling about the possibility of becoming pregnant and will be asked about your plans to have children in the future. Your options for contraception will also be explored, but you may choose whether or not you want to receive contraception. You can receive some forms of contraception from the study clinic or be referred to an appropriate clinic for contraception.

We do not know if Truvada® has an impact on the unborn baby in HIV-uninfected women who become pregnant. If you are taking PrEP and become pregnant during the course of this study, you will be counselled on the possible risks and benefits of continuing PrEP while pregnant. If you choose to discontinue the medication, you will be retained in the study unless you elect to dropout. After your pregnancy you may choose to start taking PrEP again, and will be counselled on the use of PrEP during breastfeeding.

All participants who become pregnant during the study will be referred for antenatal care.

IMPORTANCE OF NOT SHARING THE STUDY MEDICATION

Truvada® cannot be used by itself to treat individuals with HIV. It can only treat HIV if it is used with other drugs. It could be harmful for individuals who have HIV to take it. Therefore, only people who are not infected with HIV should take Truvada®. Similarly, the HIV treatment medication used in the IT arm is only for HIV infected people, and must be used every day. It is very important that you only use the study medication that you are assigned to, and that you do not share it with anyone else. If people who have not been to see a doctor take these medications, they could be harmed by the medications.

POTENTIAL RISKS AND/OR DISCOMFORTS:

- During screening and study visits, you may experience discomfort or pain when your blood is being drawn. You may also feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.
- You may become embarrassed, worried, or anxious when receiving HIV related counselling, and if you are found to be HIV infected during the course of the study, may experience anxiety or depression related to your test results.
- Although study sites will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study could become known to others, and that social harms may result, for example, you could be treated unfairly or discriminated against, or could have problems being accepted by families and/or the community.
- At study visits, study staff will ask you a series of questions to monitor your participation in the study and ensure the study is not putting you at risk. Some of these questions may request sensitive information which could make you uncomfortable. You can choose not to answer a question if you are uncomfortable and you will not be penalized.
- Risks and side effects, occurring in a minority of individuals, related to PrEP include: gastrointestinal intolerance (e.g. nausea, diarrhoea, vomiting, and flatulence), kidney problems, weakened bones and hypersensitivity.
- Risks and side effects related to IT include dizziness, headache, trouble sleeping, drowsiness, trouble concentrating, unusual dreams, gastrointestinal intolerance (e.g. nausea, diarrhoea, vomiting, and flatulence), kidney problems, weakened bones and hypersensitivity. Some participants may also experience a rash which usually goes away without having to change the treatment. Some patients may also experience allergic reactions (including swelling of the face, lips, tongue, or throat).
- We do not know if Truvada® has an impact on the unborn baby in HIV-uninfected women who become pregnant.

POTENTIAL BENEFITS:

- HIV uninfected participants will benefit from free access to PrEP during the study period, as well as access to comprehensive HIV, STI and reproductive health services.
- HIV infected participants will benefit from access to standard clinical services, in addition to immediate treatment and monitoring of clinical status.
- There may be no other direct benefits to participants in this study. However, participants and the broader community may also benefit in the future from information learned from this study.

NEW FINDINGS

You will be informed if there is any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

COSTS TO YOU

There is no cost to you for being in this study. Truvada® pills will be given to you free of charge.

WITHDRAWAL FROM STUDY

You are free to leave the study at any time. If you choose to do so, we ask that you come for one final visit.

You may also be removed from the study without your consent if the study is stopped or cancelled or if study staff feel that staying in the study would be harmful to you.

ALTERNATIVES TO PARTICIPATION

There may be other studies going on that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counselling and testing. We will tell you about those places if you wish.

For your own safety you should not be involved in more than one study at the same time that offers medication. We shall be using fingerprinting technology to ensure that no participants are involved in multiple studies where they could be harmed by receiving different medications at the same time, as well as to confirm their identity during study visits. You can participate in other studies which do not offer other medications. For instance, another study asking you to complete a questionnaire is ok.

REIMBURSEMENT

You will not receive any reimbursement for your participation in the study.

CONFIDENTIALITY

All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

This information will be reviewed by authorised representatives of Wits RHI.
The information might also be inspected by the Bill and Melinda Gates Foundation (BMGF), the National Health Research Ethics Council (NHREC), University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC) and/or the United States Food and Medicine Administration (FDA), as well as your personal doctor.

Based on the above statement, you hereby authorise me to release your medical records to Wits RHI, its employees or agents, domestic and foreign regulatory health authorities, the Bill and Melinda Gates Foundation (BMGF), the South African Medicines Control Council (MCC), the National Health Research Ethics Council (NHREC), and the University of the Witwatersrand, Human Research Ethics Committee (HREC).

These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission.

The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

RESEARCH-RELATED INJURY

The study staff will monitor your health while you are in this study. If you have any health problems or medical emergency at any stage of the study please contact the study staff to let them know. It is important that you tell the clinic staff if you feel that you have been injured because of taking part in this study.

You will be given treatment at the study clinic free of charge, and if you require medical care that the study clinic cannot provide you will be referred for additional care.

INSURANCE AND THE ABPI STATEMENT

Wits RHI, through trial insurance, will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid out by the Association of the British Pharmaceutical Industry (ABPI Guidelines), and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

Please notify the study staff immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered. If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me or other study staff. We have a copy of the ABPI Guidelines and the Insurance Certificate, should you wish to review them.

The insurance does not cover and the study sponsor will not pay for:

- Medical treatment for *other* injuries or illnesses
- Injury caused by non-observance of the protocol

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

ADDITIONAL ACTIVITIES

In-depth Interviews

At some point during the study, the staff will invite a random selection of about 70 participants to take part in interviews where they will be asked about their experiences, including reasons for participating in the study; motivators and barriers to use of the study medications; acceptability of SMS technology; perceived gaps in service delivery and their HIV prevention preferences over time.

Costing Study

During study visits at specific time points (12 months, 24 months, and study exit), study staff will collect information from participants to learn about their household, type of sex work, immigration status and income, out-of-pocket expenditures including transport and food, any time lost due to appointments at the clinic, including travel time, consultation time, and loss of income.

PARTICIPANT PROTECTION

This study has been reviewed by the Wits Human Research Ethics Committee (HREC) and the Medicines Control Council (MCC) as per Good Clinical Practice (GCP) and South African regulations.

The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants.

A copy may be obtained from me should you wish to review it. The interview component has been reviewed by the ethics committee at the London School of Hygiene and Tropical Medicine. These two ethics committees are responsible for watching over the safety and rights of people taking part in research.

SOURCES OF ADDITIONAL INFORMATION:

If you have any questions about the study, please contact one of the people listed below:

Prof. Helen Rees Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street Hillbrow Tel: 011 358 5300	Robyn Eakle Co-investigator Wits RHI, Research Centre No. 7 Esselen Street Hillbrow Tel: 011 358 5350

This study is conducted in accordance with the Department of Health Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (2006), and has received ethical approval from the University of the Witwatersrand. If you have questions about your rights as a research participant, or complaints about how you were treated or feel that the study has caused you harm, please contact:

Prof. Peter Cleaton-Jones Chairperson for the Committee for Human Research Ethics Committee University of the Witwatersrand Tel: 011 717 2301	

After you have consulted with the study doctor and/or Ethics Committee, and if they have not provided you with answers to your satisfaction, you should write to the MCC at:

The Registrar
Medicines Control Council SA
Department of Health
Private Bag X828
PRETORIA 0001
Fax: (012) 395 9201
E-mail: helam@health.gov.za and mogobm@health.gov.za

NOTIFICATION OF PERSONAL DOCTOR:

Please indicate whether you would like us to inform your personal doctor about your participation in this study

☐ Yes I want you to inform my personal doctor
☐ No I do not want you to inform by personal doctor
☐ I do not have a personal doctor.

WRITTEN PARTICIPANT INFORMED CONSENT

Participant

☐ I hereby confirm that I have been informed by the study staff member about the nature, conduct, benefits and risks of this study.
☐ I have also received, read and understood the above written information regarding the study.
☐ I understand that all participants' fingerprints will be used to confirm their identity and to ensure that no participants are involved in multiple studies.
☐ I am aware that my personal information and health information will be stored anonymously and only a few select individuals will have access to my information.
☐ I understand that I may, at any stage, without prejudice, withdraw my consent and therefore cease further participation in the project.
☐ I have had sufficient opportunity to ask questions and (of my own free will) declare permission to participate in this programme.

Signature/mark or thumbprint		Date of signature	**DD**	**MMM**	**YYYY**
Participant Name (PRINTED)		Time of signature	:		

Study Staff Member

☐ I confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Study Staff Member Name (PRINTED)		Time of signature	:		

Impartial Witness

(Applicable only when participants cannot read and/or write)

☐ I have received and read this Pre-Exposure Prophylaxis (PrEP) Intervention Enrolment Information Sheet and Informed Consent Form and any other written information provided to the participant.

☐ I have attended all verbal discussions between the study clinic staff and participant about the study.

☐ By signing, I agree that the information provided was accurately explained to and apparently understood by the participant and that informed consent was freely given.

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Witness Name (PRINTED)		Time of signature	:		

Appendix ix. TAPS Enrolment questionnaire

ELIGIBILITY – PARTICIPANT INFORMATION AND DEMOGRAPHIC SCREENING FORM

1.	Date of Birth _ _ / _ _ _ / _ _ (DD/MMM/YY) **OR** Age: _ _ (years)	
2.	Is the participant enrolled in any other research study?	[ ] YES [ ] NO
3.	What is your relationship status?	[ ] Married and living together [ ] Married and living apart [ ] Not married but living with a partner [ ] Steady partner, not married and not living together [ ] Several partners at present [ ] Single, no partners at present [ ] Divorced or separated [ ] Chooses not to answer
4.	What is your ethnic group or tribe?	_____(please list)
5.	Where were you born?	_____(please list)
6.	What is your highest level of education?	[ ] Primary [ ] Secondary [ ] Matric [ ] Tertiary –Technicon or Further Education/Training [ ] Tertiary - University [ ] Post-graduate [ ] Don't know [ ] Chooses not to answer

7.	In the past three months, have you received money and/or goods in exchange for sex?	[ ] YES [ ] NO [ ] Chooses not to answer → Note, the participant must confirm they are a sex worker in order to participate in the study.
8.	For how long have you been doing sex work here in Johannesburg/Pretoria?	Indicate (days/weeks/months/years):_____
9.	Where do you normally work from?	[ ] Hotel/Brothel [ ] Street [ ] Home (if living outside a hotel or brothel) [ ] Other (please list) _____

NOTES/COMMENTS:

_____
_____
_____
_____
_____
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_____
_____
_____
_____

DEMOGRAPHICS AND BEHAVIOUR QUESTIONNAIRE

This questionnaire aims to collect data on the participant's living status, background, HIV knowledge, sexual behaviour, ability to adhere to medications, and interactions with their environment and networks.

The Interviewer should read the italicised text in each section to the participant. The Interviewer should make sure the participant understands what each section is about and that the participant is ok to continue before moving on with questions.

Interviewer introduction:
I'm going to ask you some very personal questions. You may find these questions difficult to answer. Your answers are completely confidential. Your name will not be written on this form, and will never be used in connection with any of the information you tell me. You do not have to answer any questions that you do not want to answer, and you may end this interview at any time you want to. However, your honest answers to these questions will help us better understand your background, your needs in relation to HIV prevention/treatment (read one according to status), and how we might make services better.

Section 1: Demographics *I am going to start by asking you some questions about yourself. Please try and relax, there are no right or wrong answers. Remember that everything you tell me will be kept secret and that you can refuse to answer any question you do not wish to answer.*		
1.	How many living children do you have?	_____ Living with you _____ Living with other carers (family/friends) [ ] Chooses not answer
2.	How many people depend on your income including you?	_____ Adults _____ Children [ ] Chooses not answer

3.	Where do you currently stay?	[ ] Urban – Hotel or Brothel [ ] Urban – Flat or house [ ] Township [ ] Rural [ ] Other: _____ [ ] Chooses not answer →If NOT Hotel or Brothel skip to Q5
4.	Which Hotel or Brothel do you stay in?	Please list:_____ [ ] Chooses not answer
5.	In the past [4 weeks], did it happen that there was no food to eat of any kind in your house, because of lack of resources to get food?	[ ] Often [ ] Sometimes [ ] Never [ ] Rarely [ ] Chooses not answer
6.	In the past [4 weeks], did it happen that you or any household member went to sleep at night hungry because there was not enough food?	[ ] Often [ ] Sometimes [ ] Never [ ] Rarely [ ] Chooses not answer
7.	In the past [4 weeks], did it happen that you or any household member went a whole day and night without eating anything at all because there was not enough food?	[ ] Often [ ] Sometimes [ ] Never [ ] Rarely [ ] Chooses not answer

8.	How long have you lived where you currently stay?	[ ] less than 6 months [ ] 6 to 12 months [ ] more than 12 months [ ] Chooses not answer
9.	In the **last month**, how many nights did you spend away from where you currently stay because you were travelling (for instance to your home to see family or friends)?	_____(# days/month) [ ] Refuse to answer
10.	In the **last year**, how many nights did you spend away from where you currently stay because you were travelling (for instance to your home to see family or friends)?	_____(# nights/year) [ ] Chooses not answer
Section 2: Knowledge and Practice *In this section I will ask you some questions about your knowledge of testing and HIV*.		
11.	How old were you when you first had an HIV test?	_____(List age) [ ] Don't know [ ] Chooses not answer
12.	When did you last have an HIV test, before today?	[ ] In the past 3 months [ ] In the past 6 months [ ] In the past 12 months [ ] More than 12 months [ ] N/A, this was my first HIV test [ ] Chooses not answer

13.	FOR PREP PARTICIPANTS ONLY: You don't have HIV now, how likely do you think it is that you will get HIV in the next 12 months?	[ ] Very likely [ ] Somewhat likely [ ] Not sure [ ] Somewhat unlikely [ ] Very unlikely [ ] Chooses not answer
14.	<u>FOR IT PARTICIPANTS ONLY:</u> You have HIV now, how likely do you think it is that you will pass on HIV in the next 12 months?	[ ] Very likely [ ] Somewhat likely [ ] Not sure [ ] Somewhat unlikely [ ] Very unlikely [ ] Chooses not answer
15.	Can you know whether a person has HIV by looking at them?	[ ] YES [ ] NO [ ] Chooses not answer If yes, indicate how you would know: _____ _____ _____ _____ _____
16.	What can you do to prevent getting HIV? List all that apply (probe for traditional medicines, etc.) _____ _____ _____ _____ _____	

Section 3: Sexual Behaviour *In this section, we will discuss condom use and different partners you may have sex with. Please remember to stop me at any time to ask questions if you are unsure about anything we are discussing. Feel free to choose not to answer any question that might make you uncomfortable.*		
17.	Are the condoms you use mostly bought ones or ones you get for free?	[ ] Don't use condoms → Skip to 21 [ ] Bought [ ] Free [ ] Both [ ] Chooses not answer
18.	Do you use male condoms, female condoms, or both?	[ ] Male condoms only [ ] Female condoms only [ ] Both [ ] Chooses not answer
19.	In the past month, have you had the experience of a condom breaking while it was being used?	[ ] YES [ ] NO [ ] Chooses not answer →If NO skip to Q21
20.	What did you do when the condom broke?	[ ] Nothing [ ] Went to clinic for advice [ ] Went to clinic for post-exposure prophylaxis [ ] Took traditional herbs or medicines [ ] Cleansed the vagina [ ] Other_____ [ ] Chooses not answer

3.1 Main and/or Casual Partners

*Now I am going to ask you about your different sexual partners. You may have different types of sexual partners. One type is a **main partner**, like a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not necessarily give you money or gifts in exchange for sex. Another type is a **casual partner**, someone you might see from time to time but whom you do not consider to be someone you are in a serious relationship with. Finally, another type of partner will be your **client**, someone who gives you money or other goods/gifts in exchange for sex. You may have clients you see just once which we will call **occasional clients**, or you may have clients you see on a regular basis, which we will call **regular clients**. Can you explain back to me your understanding of what these different types of partners are? For instance, who did you last have sex with? Which type of partner would they be?*

21.	Do you have a **main** partner?	[ ] YES [ ] NO → if NO, skip to Q25 [ ] Chooses not answer
22.	In the past 7 days, how many times did you have sex with your **main** partner (including only vaginal and anal)?	_ _ _ number of times [ ] Chooses not answer
23.	How often do you use condoms with your **main** partner?	[ ] Every time [ ] Sometimes (about half the time) [ ] Never [ ] N/A [ ] Chooses not answer

24.	What are the reasons for not using condoms all the time with your **main** partner (check all applicable)?	[ ] Personal preference [ ] No condoms available [ ] Main partner refused [ ] Chooses not answer [ ] Other – please list: _____ _____ _____ _____ _____ _____
25.	Do you have a **casual** partner or partners?	[ ] YES if yes, indicate how many: _____ [ ] NO → if NO, skip to Q30 [ ] Chooses not answer
26.	In the past 7 days, how many **casual** partner(s) did you have sex with (including only vaginal and anal)?	_ _ _ number of **casual** partners [ ] Chooses not answer
27.	Thinking of the last time you had sex with a **casual** partner, how many times did you have sex with him (including only vaginal and anal)?	_ _ _ number of times [ ] Chooses not answer
28.	How often do you use condoms with your **casual** partner(s)?	[ ] Every time [ ] Sometimes (about half the time) [ ] Never [ ] N/A [ ] Chooses not answer

29.	What are the reasons for not using condoms all the time with your **casual** partner(s) (check all applicable)?	[ ] Personal preference [ ] No condoms available [ ] Casual partner refused [ ] Chooses not answer [ ] Other – please list: _____ _____ _____ _____ _____ _____
3.2 Occasional and Regular Clients (Prompt participant to remind them of the definitions for different clients – occasional and regular)		
30.	Do you have **occasional** clients?	[ ] YES [ ] NO → if NO, skip to Q36 [ ] Chooses not answer
31.	How many **occasional** clients did you see on the most recent day you worked?	_ _ _ (number of **occasional** clients) [ ] Chooses not answer
32.	How many **occasional** clients did you see in the last 7 days?	_ _ _ (number of **occasional** clients) [ ] Chooses not answer
33.	Thinking of your last **occasional** client, how many times did you have sex with him (including vaginal and anal)?	_ _ _ number of times [ ] Chooses not answer

34.	How often do you use condoms with your **occasional** clients?	[ ] Every time [ ] Sometimes (about half the time) [ ] Never [ ] Chooses not answer →If "Every time", skip to Q36
35.	What are the reasons for not using condoms all the time with your **occasional** clients (check all applicable)?	[ ] Personal preference [ ] No condoms available [ ] Client(s) refused [ ] Chooses not answer [ ] Other – please list: _____ _____ _____ _____ _____ _____
36.	Do you have **regular** clients?	[ ] YES [ ] NO → if NO, skip to Q42 [ ] Chooses not answer
37.	How many **regular** clients did you see on the most recent day you worked?	_ _ _ (number of **regular** clients) [ ] Chooses not answer
38.	How many **regular** clients did you see in the last 7 days?	_ _ _ (number of **regular** clients) [ ] Chooses not answer
39.	Thinking of your last **regular** client, how many times did you have sex with him (including vaginal and anal)?	_ _ _ (number of times last **regular** client) [ ] Chooses not answer

40.	How often do you use condoms with your **regular** clients?	[ ] Every time [ ] Sometimes (about half the time) [ ] Never [ ] Chooses not answer →If "Every time", skip to Q42
41.	What are the reasons for not using condoms all the time with your **regular** clients (check all that apply)?	[ ] Personal preference [ ] No condoms available [ ] Client(s) refused [ ] Chooses not answer [ ] Other – please list: _____ _____ _____ _____
42.	How are you usually paid for your services?	[ ] Cash [ ] Other goods (clothing, food, housing, gifts) [ ] Cash and other goods [ ] Salary [ ] Other: _____ [ ] Chooses not answer

43.	What was the price paid by your last three clients (including occasional and regular)?	1. _____ [rands] please tick: [ ] regular or [ ] occasional 2. _____ [rands] please tick: [ ] regular or [ ] occasional 3. _____ [rands] please tick: [ ] regular or [ ] occasional [ ] Chooses not answer Note - If paid with Other Goods, please list here (estimated value): _____ _____ _____ _____ _____
Section 4: Substance Use *In this section, I will briefly ask you about whether you drink or use other substances. As a reminder, these responses will be kept confidential, but please let me know if you have questions or are uncomfortable at any time.*		
44.	At what age did you first start drinking alcohol?	_____ (list age) [ ] I don't drink alcohol → Skip to Q49 [ ] Chooses not answer
45.	How often do you have a drink containing alcohol?	[ ] Monthly or less [ ] 2 to 4 times a month [ ] 2 to 3 times a week [ ] 4 or more times a week [ ] Chooses not answer

46.	How many drinks containing alcohol do you have on a typical day when you are drinking?	[ ] 1 or 2 [ ] 3 or 4 [ ] 5 or 6 [ ] 7, 8 or 9 [ ] 10 or more [ ] Chooses not answer
47.	How often do you have six or more drinks on one occasion?	[ ] Daily or almost daily [ ] Weekly [ ] Less than monthly [ ] Monthly [ ] Never [ ] Chooses not answer
48.	In the past 7 days, have you had sex with a client while under the influence of alcohol?	[ ] YES [ ] NO [ ] Chooses not answer
49.	In the past week, have you used any of the following drugs (tick all that apply)?	[ ] Tik [ ] Dagga/Marijuana [ ] Mandrax [ ] Crack or rock [ ] Nyaope [ ] Heroin [ ] Other_____ (broncleer, etc.) [ ] N/A (don't use drugs) [ ] Chooses not answer

Section 5: Sexual History and Sex Work *Now we will briefly discuss your experiences with sex and doing sex work.*		
50.	How old were you when you first had sex?	_ _ _ (Age) [ ] Chooses not answer
51.	Was your first sex act forced? ("forced" means he/multiple perpetrators physically held you down or threatened to harm you if you did not perform a sexual act)	[ ] YES [ ] NO [ ] Chooses not answer
52.	Was your first sex act coerced? ("Coerced" means feelings of being violated - for example you felt extreme pressure, he threatened to start rumours, badgering, and bribing, including the use of his physical size)	[ ] YES [ ] NO [ ] Chooses not answer
53.	How old were you when you first exchanged sex for money or other goods?	_ _ _ (Age) [ ] Chooses not answer
54.	In the last month, where did you meet or make contact with most of your clients?	[ ] Brothel/hotel [ ] Street or public place [ ] Bar [ ] Nightclub [ ] Shebeen [ ] Escort agency [ ] Through an advert (client phoned me) [ ] Other_____ [ ] Chooses not answer

55.	Where else (cities or towns) besides Johannesburg/Pretoria, if any, have you practiced sex work other than here in the last six months?	(Write down all places here)
Section 6: Health Behaviour *In this section, we will discuss where you go to get healthcare and experiences with accessing services.*		
56.	Where do you usually go when you feel sick?	[ ] Clinic [ ] Traditional healer [ ] Pastor [ ] Friend/family [ ] Stay at home [ ] Other:_____ [ ] Chooses not answer
57.	Do you go to the clinic to keep healthy, such as for HIV testing, check-ups, or other purposes?	[ ] YES [ ] NO [ ] Chooses not answer
58.	Think of the most recent time you had to take medication for several days in a row. Were you able to take the medication every day?	[ ] YES [ ] NO→If NO skip to Q60 [ ] Chooses not answer
59.	Were you able to finish all of the medication?	[ ] YES [ ] NO [ ] Chooses not answer

60.	Have you ever had difficulty getting healthcare when you tried to access it?	[ ] YES [ ] NO →If NO skip to Q63 [ ] Chooses not answer
61.	What was the reason you had difficulty accessing care?	[ ] Refused treatment/care by clinic staff [ ] Police harassment [ ] Community harassment [ ] Too expensive [ ] Could not take time off from working [ ] Long waiting times [ ] Other_____ [ ] Chooses not answer
62.	If you were refused treatment, can you tell me why?	Reason: (probe for stigma, immigration status, language barriers) _____ _____ _____ _____ _____
<u>Section 7: Violence</u> *In this section, we will briefly discuss experiences with violence you may have had with different partners. The questions in this section can be difficult to answer for some people so remember that you do not have to answer if you choose not to. First we will ask about main or casual partners. Next we will ask about clients.*		
63.	Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by your main and/or casual partner(s)?	[ ] YES [ ] NO [ ] Don't have a main or casual partner →Skip to Q67 [ ] Chooses not answer

64.	Are you afraid of your partner?	[ ] YES [ ] NO [ ] Chooses not answer
65.	Within the last year, has your main and/or casual partner(s) forced you to have sexual activities by threatening you, holding you down or hurting you in some way?	[ ] YES [ ] NO [ ] Chooses not answer
66.	Within the past year, did you seek medical attention as a result of violence you experienced from your main and/or casual partner(s)?	[ ] YES [ ] NO [ ] Chooses not answer
67.	Within the past last year, have you been slapped, kicked, or otherwise physically hurt by a client or clients?	[ ] YES [ ] NO [ ] Chooses not answer
68.	Within the last year, has a client ever forced you to have sexual activities by threatening you, holding you down or hurting you in some way?	[ ] YES [ ] NO [ ] Chooses not answer
69.	Are you afraid of any of your clients?	[ ] YES [ ] NO [ ] Chooses not answer
70.	Within the last year, did you seek medical attention as a result of violence from a client or clients?	[ ] YES [ ] NO [ ] Chooses not answer

71.	Within the past year, have you experienced violence from a police officer?	[ ] YES [ ] NO [ ] Chooses not answer
72.	Have you ever used post-exposure prophylaxis (PEP) after sexual violence?	[ ] YES [ ] NO→If NO skip to Q77 [ ] Chooses not answer
73.	Where did you go to get the PEP?	[ ] Hospital or clinic [ ] Directly from pharmacy [ ] From a friend [ ] Other _____ [ ] Chooses not answer
74.	For how long did you take the PEP?	[ ] Less than one week [ ] One to two weeks [ ] Two to three weeks [ ] Four weeks [ ] Chooses not answer
75.	Did you have any difficulty finishing the PEP?	[ ] YES [ ] NO →If NO skip to Q77 [ ] Chooses not answer
76.	If yes, please explain:	_____ _____ _____

Section 8: Social Connections

Now I am going to ask you about some of your social relationships and experiences.

77.	Do your family and/or friends know that you are a sex worker?	[ ] YES, family [ ] YES, friends [ ] YES, both [ ] NO, neither [ ] Chooses not answer
78.	Are you connected with any sex worker groups such as Sisonke or SWEAT?	[ ] YES [ ] NO→If NO skip to Q80 [ ] Chooses not answer
79.	In the past year, have you participated in any SWEAT or Siskonke activities, or the Creative Space activities through the Sex Worker Project?	[ ] YES [ ] NO [ ] Chooses not answer
80.	Do you go to any other organisations or people (family/friends) for emotional or social support?	[ ] YES [ ] NO [ ] Chooses not answer
81.	Where do you go for emotional or social support?	List: _____ _____ _____

Questions/Comments

Do you have any questions or comments about the study, the medication, or the services you will receive in the study?

_____
_____
_____
_____
_____
_____
_____

Appendix x. IDI participant information sheet and consent form

Participant No:_____

Participant Qualitative Study Information Sheet and Informed Consent Form

Study Title:

The TAPS Demonstration Project: Expanded use of ART for Treatment And Prevention for female Sex workers in South Africa

Study number	WRHI046
Study Sponsor	Wits Reproductive Health and HIV Institute
Principal Investigator	Helen Rees
Co-Investigators	Robyn Eakle, Francois Venter, Gabriela Gomez
Site Address	7 Esselen Street, Hillbrow, 2001
Site contact numbers	0616043097 / 011 358 5424

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

INTRODUCTION

Hello, my name is _____. I am a member of staff with the Wits Reproductive Health and HIV Institute (Wits RHI); an organisation associated with the University of the Witwatersrand and I am assisting with the TAPS project. You have already consented to participate in the main study, and we would like to invite to you participate in a series of interviews to help us understand your perspective of participating in the study.

This information leaflet is to help you to decide if you would like to take part in the interviews. You should fully understand what is involved before you agree to take part. If you have any questions, do not hesitate to ask me.

You should not agree to sign up unless you are satisfied with the information you receive today.

If you agree to participate in the interviews, you will be asked to sign this document to confirm that you understand what is involved.

PURPOSE OF THE INTERVIEWS

The purpose of the interviews is to understand what makes it easy or difficult to start using and to continue use of PrEP or immediate treatment.

We would also like to find out if PrEP and immediate treatment will be accepted by people who need them; to learn more about your preferred HIV prevention method to find out how easy it is to use of SMS service to support women using PrEP or immediate treatment, and to find out about any gaps in health services, including in quality of services.

PROCEDURES

A select group of participants from the main study, the TAPS demonstration project, will be asked to participate in one on one interviews over the course of the study. The participants to be interviewed will be chosen randomly, this means every participant has the same chance of being selected. Each participant who agrees to participate in the interview component will be asked to sign a separate consent form and will be reimbursed for her travel costs. There will be a total of three interviews per participant at 3, 6, and 9 months during the course of her participation in the study.

Interviews will be conducted in Setswana, isiZulu, or English, depending on your preference.

Each interview will last approximately an hour and a half. The three interviews will be conducted at different time points during the study to provide an opportunity for you and the researcher to build on the information over time. Each interview will be audio-recorded. Audio files for interviews will not contain identifying information and will be kept in a secure location until such time as they are destroyed by the researcher.

POTENTIAL RISKS:
There are no direct risks to you, however, you may become embarrassed, worried, or anxious when talking about your experiences. We are aware of this and we will respect your right to confidentiality and privacy. Your interviews will always take place in private. You do not have to answer all questions if you prefer not to.

POTENTIAL BENEFITS:
There may be no direct benefits to participants from participating in the interviews, however, participants and the community as a whole may benefit in the future from information learned from the interviews.

RIGHTS AS A PARTICIPANT IN THIS STUDY
Your decision to participate in the interviews is completely free and you can decline to be interviewed or be part of the primary study at any time, without stating any reason.

Your decision to participate in this study or in the interviews will not affect the care you receive in the clinic or your relationship to the hospital in any way.

REIMBURSEMENT
Participants who take part in the interviews will receive R50 to cover their transport costs.

CONFIDENTIALITY
All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

The information might be inspected by the Bill and Melinda Gates Foundation (BMGF), the University of the Witwatersrand, Human Research Ethics Committee (HREC), the National Health Research Ethics Council (NHREC) and the South African Medicines Control Council (MCC). Therefore, by signing this document you hereby authorise me to release your medical records to the Bill and Melinda Gates Foundation (BMGF), the South African Medicines Control Council, the National Health Research Ethics Council (NHREC) and the University of the Witwatersrand, Human Research Ethics Committee (HREC).

These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. This information will not be disclosed to any third party in addition to the ones mentioned above without your written permission.

The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists.

ETHICAL APPROVAL

The primary research study protocol, including the in-depth interviews, has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.

The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

SOURCES OF ADDITIONAL INFORMATION:

If you have any questions about the study, please contact one of the people listed below:

Prof. Helen Rees Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street Hillbrow Tel: 011 358 5300	Robyn Eakle Co-investigator Wits RHI, Research Centre No. 7 Esselen Street Hillbrow Tel: 011 358 5350

This study is conducted in accordance with the Department of Health Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (2006), and has received ethical approval from the University of the Witwatersrand. If you have questions about your rights as a research participant, or complaints about how you were treated or feel that the study has caused you harm, please contact:

Prof. Peter Cleaton-Jones Chairperson for the Committee for Human Research Ethics Committee University of the Witwatersrand Tel: 011 717 2301	

After you have consulted with the study doctor and/or Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the MCC at:

The Registrar Medicines Control Council SA Department of Health Private Bag X828 PRETORIA 0001 Fax: (012) 395 9201 E-mail: helam@health.gov.za and mogobm@health.gov.za

WRITTEN PARTICIPANT INFORMED CONSENT

☐ I hereby confirm that I have been informed about the nature, conduct, benefits and risks of agreeing to participate in the in-depth interviews connected to The TAPS Project.

☐ I am aware that the interview will be audio-taped.

☐ I am aware that the information obtained from the study, including personal details regarding my sex, age, initials and diagnosis will be anonymously processed into a report.

☐ In view of the requirements of research, I agree that the data collected during the interviews can be processed in a computerised system by the Wits Institute of the University of the Witwatersrand.

☐ I may, at any stage, without prejudice, withdraw my consent and participation in the interviews.

☐ I have had sufficient opportunity to ask questions and (of my own free will) declare permission to participate in the interviews.

Participant:

☐	Yes, I agree to participate in in-depth interviews*

☐	No, I do not want to participate in in-depth interviews

Signature/mark or thumbprint		Date of signature			
			DD	**MMM**	**YYYY**
Participant Name (PRINTED)		Time of signature	:		

***If Yes:**

☐	I agree to the audio recording of the in-depth interviews

☐	I do not agree to the audio recording of the in-depth interviews

Signature/mark or thumbprint		Date of signature			
			DD	**MMM**	**YYYY**
Participant Name (PRINTED)		Time of signature	:		

Study Staff Member

☐ I confirm that the above participant has been fully informed about the nature, conduct and risks of the in-depth interviews.

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Study Staff Member Name (PRINTED)		Time of signature	:		

Impartial Witness

(Applicable only when participants cannot read or write)

☐ I have received and read this Participant Qualitative Study Information Sheet and Informed Consent Form and any other written information provided to the participant.

☐ I have attended all verbal discussions between the study clinic staff and participant about the in-depth interview.

☐ By signing, I agree that the information provided was accurately explained to and apparently understood by the participant and that informed consent was freely given.

Signature		Date of signature			
			DD	**MMM**	**YYYY**
Witness Name (PRINTED)		Time of signature	:		

Appendix xi. TAPS IDI Guides

IDI 1 GUIDE (MONTH 3)

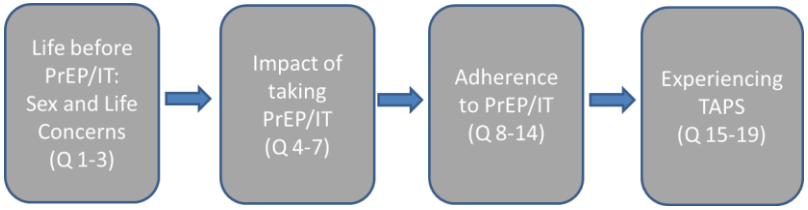
Interviewer _____ Site/Venue: _____

INTRODUCTION

This guide represents the first in a set of three interviews in which female sex workers participating in the TAPS Demonstration Project will be randomly selected and invited to participate. The primary objective of this research is to explore the individual perspectives and lived experiences of FSWs willing to take up and use PrEP or Immediate Treatment in South Africa. These serial interviews conducted by research assistants working on the project will aim to answer the following questions:

- What factors influence effective PrEP/Immediate Treatment uptake and use by female sex workers in South Africa?
- What factors should be considered for future scale-up, rollout, and implementation of PrEP/Immediate Treatment?

The questions within the interview guides feed into a larger social-ecological framework and follow a specified flow depicted in the flow chart below.



It is important while conducting the interview that the interviewer remembers the answers the participant gives as the conversation goes along in order to react appropriately to given questions and prompts. The interviewer may need to encourage the participant to speak freely and remind the participant of their previous answers. One particular aspect which may need repeated clarification is the different between clients and partners. The

definitions for clients and partners used in the demographics questionnaire is listed below for easy reference and can be read to the participant at any time.

Main and Casual Partners

*In this interview we may discuss different types of sexual partners. One type is a **main partner**, like a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not necessarily give you money or gifts in exchange for sex. Another type is a **casual partner**, someone you might see from time to time but whom you do not consider to be someone you are in a serious relationship with. Finally, another type of partner will be your **client**, someone who gives you money or other goods/gifts in exchange for sex. You may have clients you see just once which we will call **occasional clients**, or you may have clients you see on a regular basis, which we will call **regular clients**. Can you explain back to me your understanding of what these different types of partners are? For instance, who did you last have sex with? Which type of partner would they be?*

INSTRUCTIONS FOR THE INTERVIEWER – HOW TO USE THIS IDI GUIDE

1. There are 3 levels of questions:
   - Numerical research questions/topic areas highlighted in gray: the questions/areas that we as TAPS researchers want to get answers to. These don't need to be read aloud.
   - IDI questions: the questions that you as the Interviewer will ask respondents in order to get answers to the research questions. These questions will be underlined.
   - Probes: they are indicated with a bullet, and will not be translated. The interviewer should ensure that key topics listed in the probes have been addressed/discussed during the interview. So, depending on what has already been discussed, and the IDI context, you may ask these probes or not.

2. *Instructions/suggestions to interviewer are in italics and brackets [ ].*

3. The IDI guide is divided into two columns.
   - **The left-hand column** contains the research questions, IDI questions and probes. The IDI questions are suggestions for getting the discussion going. It is not required to read them verbatim, but they are written in local language to ensure some consistency across IDIs.

You may adapt the question, depending on how the interview develops, and you as the Interviewer will have to ensure that at the end the research questions have been answered. .

- **The right-hand column** is for summarising the themes brought up by the woman in the IDI. These should be summaries of the general issues raised in connection with the research question. These summaries should be more than just yes/no, but not longer than a few sentences of bullet points. They do not need to be detailed, as we have the details on the tape. **Note: the summaries and yes/no answers should be filled by the IDI interviewer immediately after the IDI.**

DAY OF INTERVIEW

First make the participant comfortable. Offer her something to drink and explain who you are and introduce yourself if you haven't met before.

Before starting the IDI, the Interviewer explains to the respondent:

Now I am going to start the recorder. [Interviewer: s*tart the tape recorder.]*

As you know from your informed consent, this IDI will be tape recorded today. Please verbally indicate that you are aware that we are tape recording this session and that it is okay with you. [*Interviewer: be sure to get a verbal okay from the respondent.]*

Today we will be discussing some of your life experiences, your experience taking PrEP/IT, and your experience coming to the clinic. There is no right or wrong answer to any of these questions so you should just tell me whatever comes to your mind. I also want to assure you that although we will be recording the interview, we will not be using your name on this tape, nor anyone else's. We will keep this recording confidential, and any information I pass back to the clinic team will not be in connection with your name. Please feel free to tell me anything you want about your experiences, positive or negative, and please tell me if there is anything you are uncomfortable with or want to skip over. We will begin now. Do you have any questions before we start?

	Research Question, IDI Questions, Probes	SUMMARY
1.	**How does HIV rank as a concern within the lives of FSWs?** When you wake up in the morning, what are your main concerns on a daily basis? • Do you worry about your family or things at home? • Do you worry about things to do with work (e.g. how do you cope, are you worried about getting sick or paying rent)? • Do you worry about your health?	
2.	**What are specific concerns the participant has around sex and HIV?** What concerns have you had about sex (both generally and in terms of clients and partners)? • Do you worry about STIs? • Do you worry about HIV? • Do you worry about your clients? • Do you worry about your other partners? • Do you have worries directly related to your work (e.g. family or friends finding out, violence?	

3.	**What does the participant do to manage concerns and what do they experience in the process (e.g. difficult partnerships, trouble negotiating protection)?** Reflecting back on what you just told me, how have you managed your concerns about sex? • What sorts of problems did you experience managing these concerns? • What did you do? • Were you able to use condoms? • Did you pick certain clients or partners over others? • Did you have sex differently (e.g. ask client or partner to pull out before ejaculation or only have anal sex)? • Do you have any specific washing practices? • Who did you talk to about your concerns or what you did to handle them?	

4.	**What were the participant's specific experiences last time she had sex without a condom?** <u>Let's talk about the last time you had sex without a condom.</u> • Who was it with? • Why did you not use a condom? • Did you talk about using a condom? • Where were you? • How did you feel afterwards (worry, etc.)? • Did you feel any different now that you are taking PrEP/IT? • Is this kind of experience something typical or different to your usual experiences with sex? • Did you do anything afterwards like washing? Or visit the clinic?	
5.	**Does the participant understand PrEP/Immediate treatment and where do they get their information? This is specifically getting at knowledge and rumours.** <u>What do you know about PrEP/IT?</u> • What is the purpose of taking PrEP/IT? • Where did you hear about it? • What have you heard from friends? • What have you heard from family? • What have you heard in the clinic? • What, if anything, have you heard people say about TAPS (this specific study)?	

6.	What might have kept the participant from starting PrEP/IT sooner? What were their initial concerns? **<u>What concerns did you have initially about PrEP/IT before you started taking it?</u>** • Were you worried about side effects? • Were you concerned about what other people might think? Why? • Did these concerns prevention you from starting the PrEP/IT sooner?	
7.	**How does the participant feel about taking PrEP/IT?** <u>What do you think and/or feel now about PrEP/IT</u> • What were your main reasons for taking PrEP/IT?	

8.	**Did the participant change her sexual behaviour after starting her medication?** Remember back to your concerns around sex you had before and how you handled them. Is the sex you have different now that you are taking PrEP/ IT? • Have you changed how often you use condoms? • Do you use different methods for contraception now? • Do you do anything different with your clients? • If you have a main partner or casual partner, have they asked you to change how you have sex? • Does it help or hinder your sexual relationships? In what ways? Increase or decrease sexual desire/pleasure? • Does it affect the level of protection and comfort with sexual practices?	
9.	**Has taking PrEP/Treatment had any effect/impact on the general health and well-being, and/or relationships?** What do you think the PrEP/IT does for you in terms of your health and well-being? • What impact has it had on your life in general? • Do you feel like it makes you feel weaker or stronger? • Does it have any effect in other aspects of your relationship with your regular partner or clients?	

10	**How does the participant take her medication? Is she taking her pills every day? Where and how?** Can you walk me through how you take your PrEP/IT? • When do you take it? • Where do you take it? • How do you remember to take it?	
11	**What problems is the participant experiencing in terms of adherence to the medication?** Have you experienced any problems in taking the medication? • Is there anything about your home environment or where you stay that makes it difficult to take your PrEP/IT? • Is there anything about your work environment or where you stay that makes it difficult to take your PrEP/IT? • Are there any people in your life who make it easy or difficult to take your PrEP/IT (e.g. friends, family members, partners, clients, police) • How do you feel supported by the clinic to take your PrEP/IT? • Do other participants help support you to take your PrEP/IT? • Is there anyone else who supports you? If so, what do they do and who helps you?	

12	**What role do side effects play, if any, on the participant's adherence to her medication?** <u>What side effects have you experienced from taking your PrEP/IT?</u> • How did you feel about the side effects? • How did you deal with them? • Have they caused you to stop taking the medication? *[NOTE: skip if previously mentioned in detail]*	
13	**Is the SMS messaging service helpful to the participant in attending the clinic and remembering to take study medication?** <u>Have you found the SMS messaging service to be useful? [*If they aren't receiving the messages or if this was discussed in detail earlier, skip to next question*]</u> • Do you receive both the visit reminders and the supportive messages? • Do the visit reminders help you get to the clinic, or do they make no difference? • Do you like the supportive messages? • If there are things you don't like about the visit reminders or supportive messages, what are they?	

14	**Has the participant disclosed product use to anyone and have they found any social support?** Have you told anyone that you are taking PrEP/IT? • Who was it? • What did they think/say? • What did you think about their reaction?	
15	**Has the participant shared their PrEP/IT with another person?** Sharing things with family and friends is part of our lives. Have you ever shared your PrEP/IT with someone else? • Who did you share it with? • Why did you share? *[NOTE: skip if previously mentioned]*	
16	**Has the PrEP/IT ever been stolen or sold?** Has anyone ever stolen your PrEP/Treatment? Or have you ever had to sell your PrEP/IT? • If you've had it stolen, who stole it and do you know why? • If you sold your PrEP/IT, why did you sell it? *[NOTE: skip if previously mentioned]*	

So we've been discussing what your experiences have been in life before taking PrEP/IT, and then what it's been like taking the medication. Now I am going to ask you about your experiences at the clinic. We are very interested in hearing any feedback you may have so we can ensure we are providing the best services possible, so please feel free to share any opinions and experiences you have.		
17	**How did the participant find out about the clinic and the study?** <u>How did you hear about the clinic?</u> • Who told you? • How did you get here? • Did you have difficulties in finding the clinic or getting to it?	
18	**What motivated the participant to come to the clinic?** <u>Why did you decide to start coming to the clinic?</u> • What's your biggest reason for coming to the clinic? • What was your reason originally and what is your reason now? • Did your friends or family encourage you to come? • Did you have any health related concerns that brought you to the clinic? • Were you interested in getting tested and taking care of your health more generally? • Did you want to get PrEP/IT specifically?	

19	**Does the participant interact with other participants? What sorts of things does she hear?** <u>What do you talk about with your friends who also come to the clinic?</u> *[If no, then skip to next question]* • Have you shared impressions of the study, medications, or clinic experiences with other participants? • If yes, how have you felt about other experiences you have heard about? • What have others said about experiences at the clinic? • Are there things you or others would change?	
20	**How does the participant feel about the clinic?** <u>Would you recommend this clinic to other people?</u> *[If no, then skip to last prompt]* • Who would you tell to come here? • Why? • What do you like most about coming to the clinic? • What would you change about the clinic? *[skip if answered above]*	

21	**How does the participant feel about PrEP/IT?** <u>Would you recommend taking PrEP/IT to other people?</u> • Who would you recommend it to? • Why? • What if PrEP/IT were available to more people than just sex workers?	
We are coming to the end of the interview now. I just have two more questions for you. These are quite broad questions so just tell me whatever comes to your mind. Remember there is no right or wrong answer, so you can answer these in any way you want.		
22	**What aspects within the participant's life most affect their perceived quality of life? Does HIV come up?** <u>If you could change one thing in your life today to make it better, what would it be?</u> Examples: • Working situation or type of work • Relationships with clients or regular partners • Friend or family relationships • Education • Health issues • Legal/policy frameworks	

23	**Any other questions?** <u>Is there anything else you would like to tell me about the study products or your experience using PrEP/Treatment?</u> • Ask if they have any questions for you	

IDI 2 Guide (Month 6)

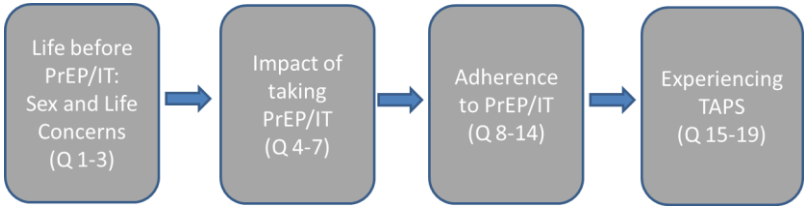
Interviewer _____ Site/Venue: _____

INTRODUCTION

This guide represents the first in a set of three interviews in which female sex workers participating in the TAPS Demonstration Project will be randomly selected and invited to participate. The primary objective of this research is to explore the individual perspectives and lived experiences of FSWs willing to take up and use PrEP or Immediate Treatment in South Africa. These serial interviews conducted by research assistants working on the project will aim to answer the following questions:

- What factors influence effective PrEP/Immediate Treatment uptake and use by female sex workers in South Africa?
- What factors should be considered for future scale-up, rollout, and implementation of PrEP/Immediate Treatment?

The questions within the interview guides feed into a larger social-ecological framework and follow a specified flow depicted in the flow chart below.



It is important while conducting the interview that the interviewer remembers the answers the participant gives as the conversation goes along in order to react appropriately to given questions and prompts. The interviewer may need to encourage the participant to speak freely and remind the participant of their previous answers. One particular aspect which may need repeated clarification is the different between clients and partners. The definitions for clients and partners used in the demographics questionnaire is listed below for easy reference and can be read to the participant at any time.

Main and Casual Partners

*In this interview we may discuss different types of sexual partners. One type is a **main partner**, like a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not necessarily give you money or gifts in exchange for sex. Another type is a **casual partner**, someone you might see from time to time but whom you do not consider to be someone you are in a serious relationship with. Finally, another type of partner will be your **client**, someone who gives you money or other goods/gifts in exchange for sex. You may have clients you see just once which we will call **occasional clients**, or you may have clients you see on a regular basis, which we will call **regular clients**. Can you explain back to me your understanding of what these different types of partners are? For instance, who did you last have sex with? Which type of partner would they be?*

INSTRUCTIONS FOR THE INTERVIEWER – HOW TO USE THIS IDI GUIDE

1. There are 3 levels of questions:
   - Numerical research questions/topic areas highlighted in gray: the questions/areas that we as TAPS researchers want to get answers to. These don't need to be read aloud.
   - IDI questions: the questions that you as the Interviewer will ask respondents in order to get answers to the research questions. These questions will be underlined.
   - Probes: they are indicated with a bullet, and will not be translated. The interviewer should ensure that key topics listed in the probes have been addressed/discussed during the interview. So, depending on what has already been discussed, and the IDI context, you may ask these probes or not.

2. *Instructions/suggestions to interviewer are in italics and brackets [ ].*

3. The IDI guide is divided into two columns.
   - **The left-hand column** contains the research questions, IDI questions and probes. The IDI questions are suggestions for getting the discussion going. It is not required to read them verbatim, but they are written in local language to ensure some consistency across IDIs. You may adapt the question, depending on how the interview develops, and you as the Interviewer will have to ensure that at the end the research questions have been answered. .

- **The right-hand column** is for summarising the themes brought up by the woman in the IDI. These should be summaries of the general issues raised in connection with the research question. These summaries should be more than just yes/no, but not longer than a few sentences of bullet points. They do not need to be detailed, as we have the details on the tape. **Note: the summaries and yes/no answers should be filled by the IDI interviewer immediately after the IDI.**

DAY OF INTERVIEW

First make the participant comfortable. Offer her something to drink and explain who you are and introduce yourself if you haven't met before.

Before starting the IDI, the Interviewer explains to the respondent:

Now I am going to start the recorder. [Interviewer: s*tart the tape recorder.]*

As you know from your informed consent, this IDI will be tape recorded today. Please verbally indicate that you are aware that we are tape recording this session and that it is okay with you. [*Interviewer: be sure to get a verbal okay from the respondent.]*

Today we will be discussing some of your life experiences, your experience taking PrEP/IT, and your experience coming to the clinic. There is no right or wrong answer to any of these questions so you should just tell me whatever comes to your mind. I also want to assure you that although we will be recording the interview, we will not be using your name on this tape, nor anyone else's. We will keep this recording confidential, and any information I pass back to the clinic team will not be in connection with your name. Please feel free to tell me anything you want about your experiences, positive or negative, and please tell me if there is anything you are uncomfortable with or want to skip over. We will begin now. Do you have any questions before we start?

	Research Question, IDI Questions, Probes	SUMMARY
	How does HIV rank as a concern within the lives of FSWs? Since we last spoke, you told me your daily concerns were XXX. Have these changed since then, in the last few months? • Do you worry about your family or things at home? • Do you worry about things to do with work (e.g. how do you cope, are you worried about getting sick or paying rent)? • Do you worry about your health?	
2.	**What are specific concerns the participant has around sex and HIV?** When we last spoke you had XXX concerns about sex, how have these changed since then? • Do you worry about STIs? • Do you worry about HIV? • Do you worry about your clients? • Do you worry about your other partners? • Do you have worries directly related to your work (e.g. family or friends finding out, violence?	

3.	**What were the participant's specific experiences last time she had sex without a condom?** Last time we spoke we discussed one of your experiences having sex without a condom. Can you tell me about an experience you've had since the last time we spoke when you had sex without a condom? • Who was it with? • Why did you not use a condom? • Did you talk about using a condom? • Where were you? • How did you feel afterwards (worry, etc.)? • Did you feel any different now that you are taking PrEP/IT? • Is this kind of experience something typical or different to your usual experiences with sex? • Did you do anything afterwards like washing? Or visit the clinic?	

4.	**Does the participant understand PrEP/Immediate treatment and where do they get their information? This is specifically getting at knowledge and rumours.** <u>Now that you've been coming to the clinic for a couple of months, can you tell me what do you know about PrEP/IT?</u> • What is the purpose of taking PrEP/IT? • Where did you hear about it? • What have you heard from friends? • What have you heard from family? • What have you heard in the clinic? • What, if anything, have you heard people say about TAPS (this specific study)?	
5.	**What might have kept the participant from starting PrEP/IT sooner? What were their initial concerns?** **<u>What concerns did you have initially about PrEP/IT before you started taking it?</u>** • Were you worried about side effects? • Were you concerned about what other people might think? Why? • Did these concerns prevention you from starting the PrEP/IT sooner?	

6.	**How does the participant feel now about taking PrEP/IT?** <u>What do you think and/or feel now about PrEP/IT</u> • What were your main reasons for taking PrEP/IT?	
7.	**Did the participant change her sexual behaviour after starting her medication?** <u>Is the sex you have different now that you are taking PrEP/ IT *[modify slightly if participant has rolled off PrEP]*?</u> • Have you changed how often you use condoms? • Do you use different methods for contraception now? • Do you do anything different with your clients *[negotiation, pricing, etc]*? • If you have a main partner or casual partner, have they asked you to change how you have sex? • Does it help or hinder your sexual relationships? In what ways? Increase or decrease sexual desire/pleasure? • Does it affect the level of protection and comfort with sexual practices?	

8.	**Has taking PrEP/Treatment had any effect/impact on the general health and well-being, and/or relationships?** <u>So far, how has the PrEP/IT influenced your health and well-being?</u> • What impact has it had on your life in general? • Do you feel like it makes you feel weaker or stronger? • Does it have any effect in other aspects of your relationship with your regular partner or clients?	
9.	**How does the participant take her medication? Is she taking her pills every day? Where and how?** <u>Can you walk me through how you take your PrEP/IT?</u> • When do you take it? • Where do you take it? • How do you remember to take it? • Has anything changed since we last spoke?	

10	**What problems is the participant experiencing in terms of adherence to the medication?** <u>Since we last spoke, have you experienced any problems in taking the medication?</u> • Is there anything about your home environment or where you stay that makes it difficult to take your PrEP/IT? • Is there anything about your work environment or where you stay that makes it difficult to take your PrEP/IT? • Are there any people in your life who make it <u>easy or difficult</u> to take your PrEP/IT (e.g. friends, family members, partners, clients, police) • How do you feel supported by the clinic to take your PrEP/IT? • Do other participants help support you to take your PrEP/IT? • Is there anyone else who supports you? If so, what do they do and who helps you?	

11	**What role do side effects play, if any, on the participant's adherence to her medication?** Since we last spoke, what side effects have you experienced from taking your PrEP/IT, if any? • How did you feel about the side effects? • How did you deal with them? • Have they caused you to stop taking the medication? *[NOTE: skip if previously mentioned in detail]*	
12	**Is the SMS messaging service helpful to the participant in attending the clinic and remembering to take study medication?** Now that it has been a couple of months, what do you think about the SMS messages? [*If they aren't receiving the messages or if this was discussed in detail earlier, skip to next question*] • Do you receive both the visit reminders and the supportive messages? • Do the visit reminders help you get to the clinic, or do they make no difference? • Do you like the supportive messages? • If there are things you don't like about the visit reminders or supportive messages, what are they?	

13	**Has the participant disclosed product use to anyone and have they found any social support?** Since we last spoke, have you told anyone that you are taking PrEP/IT? • Who was it? • Why did you decide to tell that person in particular? • What did they think/say? • What did you think about their reaction?	
14	**Has the participant shared their PrEP/IT with another person?** Sharing things with family and friends is part of our lives. Have you ever shared your PrEP/IT with someone else? • Who did you share it with? • Why did you share? *[NOTE: skip if previously mentioned]*	

15	**Has the PrEP/IT ever been stolen or sold?** <u>Has anyone ever stolen your PrEP/Treatment? Or have you ever had to sell your PrEP/IT?</u> • If you've had it stolen, who stole it and do you know why? • If you sold your PrEP/IT, why did you sell it? *[NOTE: skip if previously mentioned]*	
So we've been discussing what your experiences have been in life before taking PrEP/IT, and then what it's been like taking the medication. Now I am going to ask you about your experiences at the clinic. We are very interested in hearing any feedback you may have so we can ensure we are providing the best services possible, so please feel free to share any opinions and experiences you have.		
16	**What motivated the participant to come to the clinic?** <u>What keeps you coming back to the clinic?</u> • What's your biggest reason for coming to the clinic? • Do your friends or family encourage you to come? • Do you have any health related concerns that bring you to the clinic? • Does regular HIV testing play a big role in coming to the clinic? • Did you want to get PrEP/IT specifically?	

17	**Does the participant interact with other participants? What sorts of things does she hear?** <u>What do you talk about with your friends who also come to the clinic?</u> *[If no, then skip to next question]* • Have you shared impressions of the study, medications, or clinic experiences with other participants? • If yes, how have you felt about other experiences you have heard about? • What have others said about experiences at the clinic? • Are there things you or others would change? • Have you talked to anyone new about the clinic?	
18	**How does the participant feel about the clinic?** How do you feel about the clinic now that you have been coming for several months? Would you recommend it to any one you know? *[If no, then skip to last prompt]* • Who would you tell to come here? • Why? • What do you like most about coming to the clinic? • What would you change about the clinic? *[skip if answered above]*	

19	**How does the participant feel about PrEP/IT?** <u>Now that it's been a couple of months, would you recommend taking PrEP/IT to other people?</u> • Who would you recommend it to? • Why? • What if PrEP/IT were available to more people than just sex workers?	
We are coming to the end of the interview now. I just have two more questions for you. These are quite broad questions so just tell me whatever comes to your mind. Remember there is no right or wrong answer, so you can answer these in any way you want.		
20	**What aspects within the participant's life most affect their perceived quality of life? Does HIV come up?** <u>If you could change one thing in your life today to make it better, what would it be?</u> Examples: • Working situation or type of work • Relationships with clients or regular partners • Friend or family relationships • Education • Health issues • Legal/policy frameworks	

21	**Any other questions?** <u>Is there anything else you would like to tell me about the study products or your experience using PrEP/Treatment?</u> • Ask if they have any questions for you	

IDI Guide 3 (Month 9)

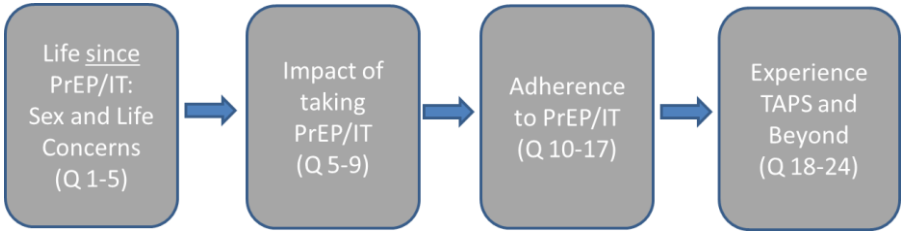
Interviewer _____ Site/Venue: _____

I. INTRODUCTION

This guide represents the third in a set of three interviews in which female sex workers participating in the TAPS Demonstration Project will be randomly selected and invited to participate. The primary objective of this research is to explore the individual perspectives and lived experiences of FSWs willing to take up and use PrEP or Immediate Treatment in South Africa. These serial interviews conducted by research assistants working on the project will aim to answer the following questions:

- What factors influence effective PrEP/Immediate Treatment uptake and use by female sex workers in South Africa?
- What factors should be considered for future scale-up, rollout, and implementation of PrEP/Immediate Treatment?

The questions within the interview guides feed into a larger social-ecological framework and follow a specified flow depicted in the flow chart below.



It is important while conducting the interview that the interviewer remembers the answers the participant gives as the conversation goes along in order to react appropriately to given questions and prompts. The interviewer may need to encourage the participant to speak freely and remind the participant of their previous answers. One particular aspect which may need repeated clarification is the different between clients and partners. The definitions for clients and partners used in the demographics questionnaire is listed below for easy reference and can be read to the participant at any time.

Main and Casual Partners

*In this interview we may discuss different types of sexual partners. One type is a **main partner**, like a husband, boyfriend, or someone you might call an emotional partner that you see regularly whom you do not see as a client and who does not necessarily give you money or gifts in exchange for sex. Another type is a **casual partner**, someone you might see from time to time but whom you do not consider to be someone you are in a serious relationship with. Finally, another type of partner will be your **client**, someone who gives you money or other goods/gifts in exchange for sex. You may have clients you see just once which we will call **occasional clients**, or you may have clients you see on a regular basis, which we will call **regular clients**. Can you explain back to me your understanding of what these different types of partners are? For instance, who did you last have sex with? Which type of partner would they be?*

INSTRUCTIONS FOR THE INTERVIEWER – HOW TO USE THIS IDI GUIDE

1. There are 3 levels of questions:
   - Numerical research questions/topic areas highlighted in gray: the questions/areas that we as TAPS researchers want to get answers to. These don't need to be read aloud.
   - IDI questions: the questions that you as the Interviewer will ask respondents in order to get answers to the research questions. These questions will be underlined.
   - Probes: they are indicated with a bullet, and will not be translated. The interviewer should ensure that key topics listed in the probes have been addressed/discussed during the interview. So, depending on what has already been discussed, and the IDI context, you may ask these probes or not.

2. *Instructions/suggestions to interviewer are in italics and brackets [ ].*

3. The IDI guide is divided into two columns.
   - **The left-hand column** contains the research questions, IDI questions and probes. The IDI questions are suggestions for getting the discussion going. It is not required to read them verbatim, but they are written in local language to ensure some consistency across IDIs. You may adapt the question, depending on how the interview develops, and you as the Interviewer will have to ensure that at the end the research questions have been answered. .
   - **The right-hand column** is for summarising the themes brought up by the woman in the IDI. These should be summaries of the general issues raised in connection with the research question. These summaries should be more than just yes/no, but not longer than a few

sentences of bullet points. They do not need to be detailed, as we have the details on the tape. **Note: the summaries and yes/no answers should be filled by the IDI interviewer immediately after the IDI.**

DAY OF INTERVIEW

First make the participant comfortable. Offer her something to drink and explain who you are and introduce yourself if you haven't met before.

Before starting the IDI, the Interviewer explains to the respondent:

Now I am going to start the recorder. [Interviewer: s*tart the tape recorder.]*

Just a reminder, as we discussed when we did your informed consent, this IDI will be tape recorded today. Please verbally indicate that you are aware that we are tape recording this session and that it is okay with you. [*Interviewer: be sure to get a verbal okay from the respondent.]*

Today we will be discussing some of your life experiences, your experience taking PrEP/IT, and your experience coming to the clinic as we have done in the past interviews. We want to see if anything has changed in your life over time and whether you have any new thoughts about taking PrEP/IT. There is no right or wrong answer to any of these questions so you should just tell me whatever comes to your mind. I also want to assure you that although we will be recording the interview, we will not be using your name on this tape, nor anyone else's. We will keep this recording confidential, and any information I pass back to the clinic team will not be in connection with your name. Please feel free to tell me anything you want about your experiences, positive or negative, and please tell me if there is anything you are uncomfortable with or want to skip over. We will begin now. Do you have any questions before we start?

	Research Question, IDI Questions, Probes	SUMMARY
	Have there been any major changes in the participant's life since she has been in the study? Since you joined the project, have you had any major life changes? • Have you had a change in your living and/or working situation? • Any changes in your family or with friends? • Any changes with partners? • Any changes in making money?	
2.	**How does HIV rank as a concern within the lives of FSWs?** What have been your daily concerns recently? Have these changed since the last time we spoke and/or since you joined the project? • Do you worry about your family or things at home? • Do you worry about things to do with work (e.g. how do you cope, are you worried about getting sick or paying rent)? • Do you worry about your health?	

3.	**What are specific concerns the participant has around sex and HIV?** Since the last time we spoke, what kinds of concerns have you had around sex? • Do you worry about particular health issues (general, STIs, HIV)? • Do you worry about your clients? • Do you worry about your other partners? • Do you have worries directly related to your work (e.g. family or friends finding out, violence?	
4.	**What does the participant do to manage concerns and what do they experience in the process (e.g. difficult partnerships, trouble negotiating protection)?** What have you done to deal with these concerns? • What sorts of problems did you experience managing these concerns? • What did you do? • Were you able to use condoms? • Did you pick certain clients or partners over others? • Did you have sex differently (e.g. ask client or partner to pull out before ejaculation or only have anal sex)? • Do you have any specific washing practices? • Who did you talk to about your concerns or what you did to handle them?	

5.	**How have experiences of violence affected the participant since she has been in the study?** How have any experiences of violence and/or abuse affected you since you joined the project? • Have you had any of these issues with clients or partners? If yes, what happened? • Have you experienced abuse from friends, family, colleagues, or others? If yes, what happened? • How have any of these experienced affected being able to take PrEP/IT? Easier or harder?	
6.	**How does the participant feel about PrEP/Immediate treatment and what do they hear potentially from others? This is specifically getting at their personal perceptions as well as knowledge and rumours.** Now that you've been taking PrEP/IT for a while, what do you think and/or feel about it? • Why do you take PrEP/IT? • What do other people say about PrEP/IT (friend, family, colleagues, clients, partners)? • What, if anything, have you heard people say about TAPS (this specific study)?	

7.	**What have been the participant's specific experiences over time in trying to maintain condom use with PrEP/IT?** <u>How has it been trying to keep using condoms now that you are taking PrEP/IT?</u> • Is it difficult? • Who do you have problems not using a condom with (client/partner) • Why did you not use a condom? • Did you talk about using a condom? • Where were you? • How did you feel afterwards (worry, etc.)? • Is this kind of experience something typical or different to your usual experiences with sex? • Did you do anything afterwards like washing? Or visit the clinic?	

8.	**Did the participant change her sexual behaviour after starting her medication?** How has sex changed for you now that you have been taking PrEP/ IT for some time *[modify slightly if participant has rolled off PrEP]*? • Have you changed how often you use condoms? • Do you use different methods for contraception now? • Do you do anything different with your clients *[negotiation, pricing, etc]*? • If you have a main partner or casual partner, have they asked you to change how you have sex? • Does it help or hinder your sexual relationships? In what ways? Increase or decrease sexual desire/pleasure? • Does it affect the level of protection and comfort with sexual practices?	

9.	**Has taking PrEP/Treatment had any effect/impact on the general health and well-being, and/or relationships?** <u>Since you've been taking it, how has the PrEP/IT changed your overall health and well-being?</u> • What impact has it had on your life in general? • Do you feel healthier or do you feel like you get sick more often? • Do you feel like it makes you feel weaker or stronger? • Does it have any effect in other aspects of your relationship with your regular partner or clients?	
10	**How does the participant take her medication? Is she taking her pills every day? Where and how?** <u>How do you continue to take your PrEP/IT every day? What are your strategies?</u> • When do you take it? • Where do you take it? • How do you remember to take it? • Have you made any changes over time to keep taking the pills?	

11	**Has the participant disclosed product use to anyone new?** <u>Since we last spoke, have you told anyone new that you are taking PrEP/IT?</u> • Who was it? • Why did you decide to tell that person in particular (or why not)? • What did they think/say? • What did you think about their reaction?	

12	**What support systems does the participant rely on to take her medication?** What support system do you have to help you to take your medication, if any? Has this changed over time? • Are there any people in your life who make it easy or difficult to take your PrEP/IT (e.g. friends, family members, partners, clients, police) • How do you feel supported by the clinic to take your PrEP/IT? • Do other participants help support you to take your PrEP/IT? • Is there anyone else who supports you? If so, what do they do and who helps you? • If things have changed, what, how, and why have they changed in terms of support systems? • Do you interact with any of the community organizations for sex workers or others (SWEAT, Sisonke, Church, etc.)	

13	**What problems is the participant experiencing in terms of adherence to the medication?** <u>Since the last time we spoke did it happen that you were unable to take the pill? What happened?</u> • Is there anything about your home environment or where you stay that makes it difficult to take your PrEP/IT? • Is there anything about your work environment or where you stay that makes it difficult to take your PrEP/IT?	
14	**What role do side effects play, if any, on the participant's adherence to her medication?** <u>Since we last spoke, what side effects have you experienced from taking your PrEP/IT, if any?</u> • How did you feel about the side effects? • How did you deal with them? • Have they caused you to stop taking the medication? *[NOTE: skip if previously mentioned in detail]*	

15	**Is the SMS messaging service helpful to the participant in attending the clinic and remembering to take study medication?** Now that it has been a couple of months, what do you think about the SMS messages? [*If they aren't receiving the messages or if this was discussed in detail earlier, skip to next question*] • Do you receive both the visit reminders and the supportive messages? • Do the visit reminders help you get to the clinic, or do they make no difference? • Do you still like the supportive messages? • If there are things you don't like about the visit reminders or supportive messages, what are they?	
16	**Has the participant shared their PrEP/IT with another person?** Sharing things with family and friends is part of our lives. Have you ever shared your PrEP/IT with someone else? • Who did you share it with? • Why did you share? *[NOTE: skip if previously mentioned]*	

17	**Has the PrEP/IT ever been stolen or sold?** <u>Has anyone ever stolen your PrEP/Treatment? Or have you ever had to sell your PrEP/IT?</u> • If you've had it stolen, who stole it and do you know why? • If you sold your PrEP/IT, why did you sell it? *[NOTE: skip if previously mentioned]*	
So we've been discussing what your experiences have been in life before taking PrEP/IT, and then what it's been like taking the medication. Now I am going to ask you about your experiences coming to the clinic, and new policies coming online. We are very interested in hearing any feedback you may have so we can ensure we are providing the best services possible, so please feel free to share any opinions and experiences you have.		
18	**Why does the participant continue to come to the clinic?** <u>What keeps you coming back to the clinic?</u> • What's your biggest reason for coming to the clinic? • Do your friends or family encourage you to come? • Do you have any health related concerns that bring you to the clinic? • Does regular HIV testing play a big role in coming to the clinic? • Did you want to get PrEP/IT specifically?	

19	**What barriers does the participant face in trying to come to the clinic?** What are some problems you have had with coming to the clinic for your appointments? • Do you miss the appointments to pick up your PrEP/IT, or to come for your clinic visit more often? • Do transport issues get in the way of coming to the clinic? Are you coming from far away? • What about leaving where you work/live, does that sometimes cause an issue? • Or needing to pay rent?	
20	**Does the participant interact with other participants? What sorts of things does she hear?** What do you talk about with your friends who also come to the clinic? *[If no, then skip to next question]* • Have you shared impressions of the study, medications, or clinic experiences with other participants? • If yes, how have you felt about other experiences you have heard about? • What have others said about experiences at the clinic? • Are there things you or others would change? • Have you talked to anyone new about the clinic?	

21	**How does the participant feel about the project and being a part of it?** How do you feel about being a part of the project now that you have been coming for a while? *[If no, then skip to last prompt]* • What have been the best and worst parts? • Would you recommend it to any one you know? • Who would you tell to come here? • Why? • What do you like most about coming to the clinic? • What would you change about the clinic? *[skip if answered above]*	
22	**What does the participant think about the national rollout of PrEP/IT?** What do you think about PrEP and IT being given to everyone coming to the sex worker clinics? *[explain new policy if she doesn't already know]* • Do you think other sex workers will want these interventions? Why or why not? • Would other people like to take PrEP or IT? If so, who? • Do you already know clients or partners who want PrEP or IT? • Do you know any sex workers not coming to the clinic who want PrEP or IT? If so, why aren't they coming?	

We are coming to the end of the interview now. I just have two more questions for you. These are quite broad questions so just tell me whatever comes to your mind. Remember there is no right or wrong answer, so you can answer these in any way you want.		
23	**What aspects within the participant's life most affect their perceived quality of life? Does HIV come up?** <u>If you could change one thing in your life today to make it better, what would it be?</u> Examples: • Working situation or type of work • Relationships with clients or regular partners • Friend or family relationships • Education • Health issues • Legal/policy frameworks	
24	**Any other questions?** <u>Is there anything else you would like to tell me about the study products or your experience using PrEP/Treatment?</u> • Ask if they have any questions for you	

Appendix xiii. Published TAPS Protocol – BMJ Open

Open Access Protocol

BMJ Open

Treatment And Prevention for female Sex workers in South Africa: protocol for the TAPS Demonstration Project

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ABSTRACT

Introduction: Updated guidelines from the WHO recommend antiretroviral treatment for adults with HIV at any CD4 count and daily oral pre-exposure prophylaxis (PrEP) for people at substantial risk of HIV infection. However, implementation challenges may hinder the ability of programmes to translate these recommendations into successful practice. This demonstration project is the first to integrate PrEP and immediate treatment (ITx) for female sex workers (FSWs) in South Africa to answer operational research questions.

Methods and analysis: This is a prospective cohort study where the main outcome is retention at 12 months. The study population is recruited into two arms across two urban sites: (1) PrEP for HIV-negative FSWs (n=400) and (2) ITx for HIV-positive FSWs with CD4 greater than national guidelines (n=300). We investigate process and other health indicators, uptake and use of PrEP and ITx through qualitative research, and evaluate cost-effectiveness analysis combined with estimates of impact through epidemiological modelling.

Ethics and dissemination: The *Treatment And Prevention for female Sex workers in South Africa (TAPS) Project* was designed as an implementation study before emtricitabine/tenofovir disoproxil fumarate was licenced as an indication for PrEP in South Africa. Therefore, clinical trial requirements for ethical and South African Medicines Control Council approvals were followed. Results will be disseminated to participants, local health officials and other stakeholders, as well as in peer-reviewed journals and at conferences.

Strengths and limitations of this study

- The *Treatment And Prevention for female Sex workers in South Africa* study incorporates a multidisciplinary service delivery evaluation within an implementation science paradigm.
- Success will be measured using several outcomes enabling triangulation of data.
- The study was designed to adapt to shifts in South African antiretroviral therapy guidelines and clinical standards.
- The study will not measure the effectiveness of any service delivery model as there is no comparison arm.
- Our sample size is relatively small and might not be representative of the national population of female sex workers.

INTRODUCTION

Globally, UNAIDS data have shown a significant and continuous decline (35%) in the number of new HIV infections since 2000.[1] In sub-Saharan Africa, this trend is even more pronounced with a 41% decline. However, in this region of the world, where women make up for more than half of all people living with HIV, incidence rates remain high.[1] In particular, the HIV epidemic in South Africa continues to be the highest in the world, based on both HIV incidence (with a currently estimated rate of up to 4 per 100 women-years[2 3]) and total number of people living with HIV (6.8 million estimated in 2014.[4 5]

The South African National Strategic Plan on HIV, sexually transmitted infections (STIs) and tuberculosis for 2012–2016[6] prioritises interventions with the aim to reduce new infections on a national level by 50% using combination prevention while scaling up treatment to cover at least 80% of the population. It also identifies key populations as a major focus of the strategy, which calls for a multifaceted approach to ending the epidemic. Sex workers are among the key populations identified in the past and current National Strategic Plans. Globally, female sex workers (FSWs) are 13.5 times more likely to be living with HIV than women in the general population.[7] The 2013 South African Key Populations Report estimates that HIV prevalence among FSWs is between 44 and 69%,[8–11] with 19.8% of all new infections being attributed to sex work, including infections among clients and partners of clients.[12]

A study conducted in 2008 in a cohort of high-risk women in KwaZulu-Natal Province, estimated incidence to be as high as 7.2/100 person-years.[11] More recently, a prevalence study conducted among populations of sex workers found a 72% HIV prevalence with low treatment uptake in Gauteng Province.[13] This high vulnerability is rooted in the many structural drivers of HIV risk affecting this population including: restricted access to healthcare, criminalisation and lack of legal protection, unsafe working conditions, stigma, and economic hardship.[12] As a marginalised population who are stigmatised and criminalised, sex workers require specialised programmes sensitive to their needs for interventions in HIV prevention, care and treatment as well as support to access other health and legal services.

Following the positive results of antiretroviral (ARV)-based prevention studies in reducing both HIV transmission (through ITx) and acquisition (through PrEP),[14–20] global and national authorities updated HIV guidelines to recommend antiretroviral therapy (ART) be initiated at any CD4 count in adults and daily oral PrEP as an additional prevention strategy for people at substantial risk of HIV infection.[21–28] While modelling studies have shown that the scaling up of new prevention and treatment tools across the HIV continuum of care could have a significant impact on the epidemic,[24–26] implementation challenges relating to health service capacity, acceptability and financing and resource allocation may hinder the ability of the programmes from making a significant difference to the HIV epidemic.[27 28]

The evaluation of existing and innovative models of care to implement new technologies for prevention and treatment through demonstration projects is being conducted around the world.[29] These projects represent a spectrum of designs from clinical trial-like protocols to 'real-world' implementation science studies, yet all have similar goals: to test delivery models of new technologies and interventions to inform policy and programming. In particular, projects tend to cater to key populations where acceptability and uptake of technologies such as oral PrEP may be higher and intersect with those populations who might benefit the most initially, such as men who have sex with men, sex workers, serodiscordant couples and young women. These prevention-focused projects are situated within a landscape of evolving HIV treatment guidelines, as treatment is now recognised as the major contributor to prevention and thus many include treatment components.[21 30]

The demonstration project described here is the first to integrate a combination prevention intervention including oral PrEP and ITx (for those with CD4 counts higher than current national guidelines) for FSWs in South Africa.[i] The interventions are being delivered at two clinic-based sites for FSWs in Gauteng Province. Gauteng is the most densely populated province of South Africa, also home to both the economic and political capitals of the country.[31] This implementation study seeks to understand the 'real-world' implications of introducing PrEP and ITx into an existing service delivery structure. By combining PrEP and ITx, we aim to leverage, in a novel way, the service delivery areas needed to support these programmes which primarily include outreach for testing and counselling and clinic services. The overall aim will be to answer operational questions: whether FSWs will accept ITx or combination prevention including PrEP, whether the service delivery mechanism is capable of handling the increase in resource needs these interventions might lead to, and what kind of implications this strategy would have on overall costs, should they be considered for scale up.

METHODS AND ANALYSIS

Population and setting

FSWs are the study population defined as women self-identifying as sex workers, and who have received goods or money in exchange for sex in the past 3 months, age 18 or above, operating in the areas surrounding two existing clinics providing services for sex workers in Hillbrow, Johannesburg and the central business district in Pretoria. These clinics are run by Wits Reproductive Health and HIV Institute (RHI), one of the largest research Institutes of the University of Witswatersrand; since 1994, Wits RHI has pioneered health programmes with a strong community focus. The Hillbrow site is connected to the Esselen Clinic which is home to the well-established Wits RHI Sex Worker Project.[32] The Sex Worker Project is a comprehensive reproductive health, HIV and STI prevention and treatment service programme partnered with City of Johannesburg and the South African Department of Health (DoH). It provides services such as: HIV counselling and testing and condom distribution, nurse-initiated and managed ART (NIMART), tuberculosis screening, human papillomavirus screening, clinical services for minor ailments, psychosocial support and referrals to both clinical and legal services. The programme accesses several brothels, with mobile units to serve street-based sex workers and a stationary clinic space. The actual clinic space for the *T*reatment *A*nd *P*revention for female *S*ex workers in South Africa (TAPS) Demonstration Project is located in the Wits RHI Research and Training Centre, which is adjacent to the Esselen Clinic. At the time we initiated the study, renovations at the Esselen Clinic had begun and the building was closed which is the reason for housing the TAPS Project in the Research Centre.

The Pretoria site is located in Sediba Hope Medical Centre, a private non-profit clinic affiliated with the Department of Health, which has been serving the local community in the heart of the inner city of Pretoria. Wits RHI's Sex Worker Project has now opened a sex

[i]Recently (June 2016), the NDoH started the piloting at 10 sites of new National guidelines for treatment, where all people infected with HIV independent of their CD4 count are eligible and pre-exposure prophylaxis is available for female sex workers. This demonstration project is informing the roll out pilot directly.

Table 1 Sample size considerations

PrEP arm			ITx arm		
Retention at 12 months (%)	Precision (%)	Number	Retention at 12 months (%)	Precision (%)	Number
65	2.5	1398	75	2.5	1152
65	**5.0**	**350**	**75**	**5.0**	**288**
65	7.5	155	75	7.5	128
65	10.0	87	75	10.0	72

Numbers in bold are the numbers taken to develop the sample size.
ITx, immediate treatment; mo, months; N, number; PrEP, pre-exposure prophylaxis.

worker clinic at Sediba Hope which is also linked to the Community Health Clinic in the same building.

Design

The study design is a prospective, observational cohort study, with two study arms:

1. PrEP intervention as part of a combined prevention approach for recently documented HIV-negative FSWs;
2. ITx intervention for HIV-positive ART-naïve FSWs not eligible for ART at the currently implemented CD4-defined standard of care.

The PrEP intervention arm will seek to protect HIV-negative FSWs from acquiring HIV through the use of PrEP and other available prevention options (such as condoms). The ITx intervention arm will seek to link FSWs directly to care to reduce and avoid loss to follow-up within the treatment cascade. Indirectly, it will seek to prevent HIV-positive FSWs from transmitting the virus to clients and other sex partners through the use of ARVs.

Sample size and eligibility criteria

Table 1 shows the sample size considerations for both study arms. We aim to enrol 400 FSWs in the PrEP arm of the study. With an expected retention rate of 65% (precision of ±5%) at 12 months, we need 350 participants, which we have increased to 400 to account for variability across the two sites. To achieve this sample size, we should aim to screen 1600 FSWs, of which 800 are expected to be HIV-negative (assuming an HIV prevalence of 50%) and we estimate conservatively that 50% accept to participate. For the ITx arm, we aim to enrol 300 FSWs with an expected retention rate of 75% (precision of ±5%) at 12 months, assuming a 25% default rate which reflects recent research on the treatment cascade.[38] To achieve this sample size, we should aim to screen 3600 FSWs, of which 1800 are expected to be HIV-positive (assuming an HIV prevalence of 50%), one-third with CD4 counts over 350 (n=600) and 50% accept to participate. In practice, the screening process is a joint step in the recruitment of both the PrEP and the ITx arms. As such, we will aim to screen 3600 FSWs to be able to achieve the required sample sizes. PrEP enrolment will stop as soon as the required sample size is achieved. Note that the original calculations for this study were performed assuming a national CD4 count initiation threshold of 350.

A summary of eligibility criteria is presented in table 2. We excluded patients at risk of documented serious side effects of the regimes used. This includes patients with abnormal kidney function (eg, a creatinine clearance rate above 60.0 mL/min), taking medication for multidrug-resistant tuberculosis, testing positive for hepatitis B (PrEP only) or being prescribed any other drugs contraindicated for taking with any of the drug regimens prescribed in the study. Patients are also excluded at clinician's discretion according to their assessment of the patient's safety. We also exclude FSWs pregnant at enrolment. All pregnant women are referred to antenatal care, where HIV-positive FSWs are started on ART as per guidelines and HIV-negative FSWs counselled.

Intervention

Recruitment

Participants for both arms of the study are recruited from the local Wits RHI Sex Worker Project clinics as well as the surrounding community, and in particular places of business such as hotels/brothels, bars and streets. We leverage the existing peer educator-based outreach services currently provided by the Sex Worker Project to reach out and inform them of the study. Each potential participant completes a DoH HIV counselling and Testing (HCT) consent form first as part of standard HCT practice, to determine HIV status through the

Table 2 TAPS Project eligibility criteria

PrEP arm	ITx arm
18 years or older	18 years or older
Creatinine clearance above 60.0 mL/min	Creatinine clearance above 60.0 mL/min
Negative for hepatitis B	CD4 count above national standard for ART initiation
Not pregnant	Not pregnant
Not presenting signs or symptoms of or taking medication for MDR-TB	Not presenting signs or symptoms of or taking medication for MDR-TB
Not prescribed other drugs contraindicated for taking with emtricitabine and tenofovir disoproxil fumarate (FTC/TDF)	Not prescribed other drugs contraindicated for taking with tenofovir disoproxyl fumarate/lamivudine/ emtricitabine/efavirenz (TDF +3TC/FTC+EFV)

ART, antiretroviral therapy; ITx, immediate treatment; MDR-TB, multidrug resistant tuberculosis; PrEP, pre-exposure prophylaxis.

point-of-care rapid testing process. Discordant HIV rapid test results are then confirmed using ELISA using standard local algorithms (ie, algorithm: two rapid tests are performed simultaneously for confirmation. In case of discordant, indeterminate or positive results, blood is drawn for an ELISA).[34] Once HIV status is established, participants sign either the PrEP or ITx TAPS study informed consent form according to HIV status. Participants in the PrEP arm are counselled and informed about adherence and effectiveness of PrEP, the need to use condoms with PrEP in order to ensure a high level of protection against HIV infection as well as to prevent STIs and unwanted pregnancies. Participants in the ITx arm are also counselled about adhering to their treatment regimens and using condoms.

We aimed to balance the 'real world' aspect of the demonstration project with the consent and information gathering needs for research purposes. Therefore, at the screening visit, participants are asked to complete a demographic and behaviour questionnaire, as well as a short medical history for screening purposes. Blood samples are taken for creatinine levels, hepatitis B, syphilis testing, HIV confirmation with ELISA and viral load testing. All participants also take a point-of-care pregnancy test as part of eligibility requirements.

Participants are asked to return in 1-week, within a maximum window of up to 30 days if needed, after the screening visit for enrolment if eligible. At the enrolment visit, participants are scheduled for regular study visits to monitor medication adherence and safety. We also take a clinical history, offer syndromic STI screening and any other clinically indicated assessments such as for cervical cancer as per DoH guidelines. Potential participants are asked about fertility intentions; however, future pregnancy plans are not a part of study exclusion. Contraception is offered to those requiring a method as per standard of care, but use of a contraceptive is not a requirement for study eligibility.

The participants have access to counselling services, as well as all other services provided by the Sex Worker Project as standard of care, including but not limited to reproductive health services, referrals for legal services, substance use and violence counselling and support and post-rape care. Support groups are not currently planned as an official service of this study; however, FSWs may elect to form support groups and project staff make an effort to support this with space if requested.

Medication and adherence

HIV-negative participants fulfilling all eligibility criteria are started on co-formulated emtricitabine and tenofovir disoproxyl fumarate FTC/TDF (Truvada) in the PrEP arm. The medication for the ITx arm is tenofovir disoproxyl fumarate plus lamivudine/emtricitabine plus efavirenz combination (TDF+ 3TC/FTC+EFV), or Atripla, as per current guidelines. The drugs for the TAPS study have been donated by Gilead.

We measure adherence to PrEP through several modes of self-report as well as plasma drug level testing. Treatment adherence is measured through self-report and monitoring viral load suppression.

As adherence support, all participants have the option to receive SMS. Two types of SMS may be sent to participants. The first type is visit reminders, three sent per visit—two as reminders before the visit and one to thank the participant for attendance or to remind them to reschedule if they missed a visit. The second type is aimed at providing information and support on a weekly basis and within the following themes—adherence/side-effects/informational, health education, healthy living, referral services and affirmations. All participants are offered each type of messaging services and those who are willing to participate sign an additional consent form. Participants are able to opt out at any time and feedback on the utility of the messages is solicited throughout the study.

Management of pregnancy

Guidance from major organisations, such as the WHO and Centers for Disease Control and Prevention (CDC), USA, has made surveillance of PrEP use in pregnancy a priority.[35 36] If a participant becomes pregnant during the course of the project in the PrEP group, she will be given the option to either continue or discontinue taking PrEP. If she decides to discontinue PrEP, she will be given the option to remain in the project using other HIV prevention options, but is referred for antenatal services or termination of pregnancy services as selected. The potential for harm due to unknown risks of taking PrEP while pregnant is noted in the main study's informed consent forms.

If a participant in the treatment group becomes pregnant during the course of the project, she will also be given the option to remain in the study and be referred for antenatal services, where participants will continue lifelong treatment as per the current guidelines. If the participant decides to discontinue participation in the study, she will be referred to the clinic of her choice for continued treatment.

Follow-up visits and loss to follow-up

Participants are scheduled for clinic visits on a 3-month basis and receive a prescription refill once a month in both arms. Monitoring visits include HIV testing (PrEP arm only), CD4 and viral load tests (ITx arm only), creatinine levels, syndromic screening and treatment for STIs as required, and adherence counselling. All these services are standard of care for monitoring patients on treatment and are the minimum monitoring requirement in the newly published PrEP and ITx guidelines.[28] At each scheduled visit, participants are asked to complete a short questionnaire to record any side effects, changes in risk behaviour, fertility intentions, time of last menstrual period and adherence to ARVs. Participants may also request an unscheduled visit to report safety

events at any time. We are not collecting quantitative information on diversion of medications (eg, selling or giving ARVs to others), but we are both collecting qualitative information on this important issue as part of the in-depth interviews (IDIs) and providing intensive adherence counselling.

Loss to follow-up is defined as a participant missing two consecutive visits with no contact. Efforts will be made to contact participants by phone in the PrEP and ITx arms to understand the reasons for missed visits. However, only additional efforts, which may include a home visit, will be made to encourage participants in the ITx arm to return. If participants are contacted in the PrEP group and decide not to return, we will ask if they are willing to participate in a brief exit interview to understand the reasons for dropout and to ensure there are no safety concerns.

Final visit and withdrawal from the project

At the final project visit, all participants will be asked to answer final behavioural, violence and participant costing questionnaires. Those in the PrEP arm will have creatinine test, STI screening and treatment as necessary; while those in the treatment arm will have CD4 and viral load tests, creatinine test, STI screening and treatment as necessary, and counselling for continued adherence to their treatment regimen. They will be offered a choice to remain at the same clinic for continued care and treatment, or be transferred to another clinic of their choice. If a participant in the PrEP arm sero-converts, we will offer a full resistance testing. The participant will not be rolled on to the ITx arm but will be offered a choice to remain at the same clinic for continued care and treatment, or be transferred to another clinic of their choice. All participants will also be informed as to when they can expect a report of the project's results.

As of 1 June 2016, PrEP and the test and treat approach has been prioritised for sex workers. As a result, we are now able to transition all of the women in our study to PrEP and HIV treatment services in our Sex Worker Programme or to other clinics of their choosing offering these services, either at the end of the study or should they choose to leave the study early for any reason.

For ease of reference, we mapped all events and provided a visit schedule for both PrEP arm and ITx arm in the online supplementary appendix.

Analysis

The project is being evaluated through a mixed methods approach. This approach examines the deliverability of the interventions and their integration into a comprehensive prevention and treatment package, and includes quantitative analysis of process and questionnaire data (behaviours, uptake, linkage and retention in care and adherence), qualitative assessment of providers and user feedback on the interventions, and an economic evaluation from a societal perspective.

Quantitative analysis of process and questionnaire data

The primary outcome for both arms is the number of women retained at 12 months of follow-up (a participant is considered retained at 12 months if she attended a scheduled follow-up visit between 10.5 and 13.5 months after enrolment). In the PrEP arm, we note that a participant is considered retained even if not on PrEP but continuing the combination prevention visits. Secondary outcomes for both arms are shown in table 3.

We can expect three types of bias in cohort studies: selection bias, information bias and misclassification bias. It is possible that participants 'auto-select' (ie, a selection bias), meaning that those FSWs feeling most vulnerable will be most likely to enrol and continue participation. Since this is a demonstration project, we expect participants to decide whether to participate based on their risk perception and we will aim to document these motivations and perceptions as much as possible through qualitative research. We do not expect an information bias to be present as we are collecting the same information for all participants. Finally, misclassification could arise from a participant being considered not retained in care as per her participation in our study; however, she might be in care at another clinic. We will aim to ascertain if this is a potential bias while contacting by phone those participants missing two consecutive clinic visits in either the PrEP or the ITx arm to understand the reasons for missed visits.

Qualitative research

Data from qualitative research conducted during the PrEP efficacy trials indicate multiple and varying reasons for lack of adherence on the part of participants, thus illustrating the imperative to understand how PrEP may be best implemented in a given context from the point of view of potential consumers.[37 38] In this regard, we are conducting a multifaceted qualitative research with participants from the two project arms as well as providers at the clinics to gain perspectives on using and implementing PrEP and ITx. Methods include IDIs with participants, waiting-room observations and provider group discussions. These methods will serve as a means to compare and contrast sources of data to develop a narrative as to the feasibility, and more specifically, the motivations and barriers of implementing PrEP and ITx. We will also be able to compare these qualitative data with data from the structured questionnaires to explore different aspects of adherence to medication. All data collection tools have been piloted and adjusted as required.

Participant IDIs

We use an adapted socioecological model as a framework to explore themes related to motivations and barriers to the use of PrEP and ITx based on the multiple spheres influencing women's lives from community, household, work and clinic settings. A subset of women from the PrEP and ITx arms are being randomly invited to participate in the qualitative research component in

Table 3 TAPS Project secondary outcomes

Variable	PrEP arm	ITx arm	Type of data
Knowledge	Assessment of HIV knowledge including PrEP	Assessment of HIV knowledge including ITx	Qualitative data (IDIs) and questionnaire data
Uptake and acceptability	Description of reasons for ineligibility after first eligibility assessment	Description of reasons for ineligibility after first eligibility assessment	Questionnaire data, complemented by qualitative data
	Proportion of women accepting PrEP at baseline	Proportion of women accepting ITx at baseline	Programme data, complemented by qualitative data
	Comparison demographic characteristics of women accepting PrEP vs refusing at baseline	Comparison demographic characteristics of women accepting ITx vs refusing at baseline	Questionnaire data
Retention	Proportion of women retained and adherent to PrEP at 3, 6, 18, 24 months	Proportion of women retained and adherent to ART at 3, 6, 18, 24 months	Programme data
Patterns of use	Proportion of women using PrEP continuously for 12 months	NA	Programme data
	Description of length of use and repetitive uptake for women not using PrEP continuously for 12 months		Programme data and IDIs
Adherence	Proportion of women reporting taking >85% of pills (self-reported) at each routine visit during 12 months	Proportion of women reporting taking >85% of pills (self-reported) at each routine visit during 12 months	Questionnaire data
	Proportion of women with drug level detectable in plasma at 12 months	Proportion of women with undetectable viral load at 12 months	Clinical (laboratory) data and IDIs
Side effects	Number (by type) of all side effects reported at routine visits for 12 months	Number (by type) of all side effects reported at routine visits for 12 months	Clinical data, IDIs and clinic observations
HIV status	Number of seroconversion cases at 12 months and description of all resistance profiles	Proportion of women with plasma HIV-1 RNA level≥1000 copies/mL at 6 months or after initial suppression and description of all resistance profiles	Clinical (laboratory) data
Pregnancy	Pregnancy rates during follow-up	Pregnancy rates during follow-up	Clinical data
Sexual behaviour	Comparison of proportion of women reporting consistent condom use (stable partners, regular/new clients): baseline vs PrEP use after 12 months	Comparison of proportion of women reporting consistent condom use (stable partners, regular/new clients): baseline vs ART use after 12 months	Questionnaire data and IDIs
	Proportion of women presenting with STI symptoms at each routine visit during 12 months	Proportion of women presenting with STI symptoms at each routine during 12 months	Questionnaire data
Cell phone technology for adherence support	Proportion of women opting-out of SMS reminders at baseline and throughout the duration of the project	Proportion of women opting-out of SMS reminders at baseline and throughout the duration of the project	Programme data and IDIs
Cost of intervention	Cost per person-year on PrEP (health service perspective)	Cost per person-year on ITx (health service perspective)	Costing data
	Cost per person-year on PrEP (participant perspective)	Cost per person-year on ITx (participant perspective)	Costing questionnaire data

ART, antiretroviral therapy; IDIs, in depth interviews; ITx, immediate treatment; NA, not applicable; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

each arm (up to 40 for PrEP and up to 30 for ITx). Each participant is asked to sign a separate consent form and is reimbursed for her travel costs since this will be outside of regular clinic visit requirements. This is the only form of participant reimbursement offered since the purpose of the TAPS project is to assess retention in the programme in a 'real-world' clinic setting. Interviews are conducted individually with each participant by a research assistant who is conversant in the participant's language.

Interviews will be conducted longitudinally at months 3, 6 and 9 for each participant in order to explore themes emerging over time.[37] Interview questions will seek data related to reasons for participating in the

study, motivations and barriers to uptake and use of the interventions, acceptability of the SMS technology, perceived gaps in service delivery and HIV prevention method preferences over time. Interviews will be audio taped, and later translated into English, as needed, and transcribed.

Waiting-room observations

Informal conversations held by participants in settings such as waiting-rooms have provided invaluable information for the triangulation of qualitative data thus enriching narratives of participant behaviour during studies.[37] We are conducting waiting-room observations at the two project sites for a period of 1-week on a quarterly basis. Permission to conduct these observations is obtained from the clinic managers, and researchers conducting the observations provide study participants in the waiting-rooms with notification of who they are, what they are doing and for what purpose. The purpose of these observations is to gather informal data on participants' perspectives of the study, the interventions and issues they may be experiencing that influence their interest in the programme and ability to maintain participation. Information will be recorded in the researcher's field notebook and later uploaded into NVIVO for coding and analysis.

Provider group discussions

A recent guidance illustrates the importance of service delivery providers as an important target group for promoting and managing the dissemination and uptake of PrEP.[39] As such, we are convening informal group discussions at each site in order to explore provider experiences, including primarily the community health workers/counsellors, nurses, pharmacists, coordinators and medical officers, in delivering PrEP and ITx. All potential provider-participants are asked to complete the informed consent process and have the option to decline participation. The research is being conducted by an external contractor and does not include evaluation of providers on performance. As themes for discussion may evolve over time, a more structured discussion guide is being used initially and subsequent guides will build on emerging themes.

Analysis

All qualitative research components will be analysed using thematic analysis as defined by Braun and Clarke.[40] This approach to thematic analysis features a six-phase process: familiarisation with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and finally producing the report. Translated and transcribed transcripts from the IDIs, waiting-room observations and provider group discussions will be uploaded into NVIVO software and coded according to the coding manual created. Researchers will assemble the coding manual first by developing overarching data categories based on research objectives, then by systematic and iterative review of the data to elicit primary and subthemes. We will aim to have at least two coders per transcript. Any discrepancies in coding will be discussed between the coders with input from the senior investigator to gain consensus. Once all the data have been coded, researchers will synthesise the findings to explore commonalities and differences across participant perspectives.

Economic evaluation

The introduction of an integrated HIV prevention and care service is likely to involve several trade-offs between costs and efficiencies. We are measuring empirically the costs for participants and the healthcare providers in the two sites of the TAPS study to then model total costs, impact and cost-effectiveness of this intervention both in our cohort and at a population level. The evaluation is carried out from a societal perspective.

Healthcare provider costs

All costs will be estimated using an ingredient costing approach to define the cost per person receiving each service. Data are collected through directly observed resource use (observations of practice at sites and interviews with the healthcare workers before implementation, at early stages of implementation and 1-year after the interventions are implemented). We also review clinic costs (such as utility bills) over the duration of the study. We include capital costs (equipment, buildings, non-recurrent training), as well as recurring costs (personnel, supplies, operations and maintenance of buildings) in our estimates. We aim to include costs incurred above the direct service level, such as monitoring and evaluation and coordination costs as well as cost incurred during start up activities such as community mobilisation and training before the service delivery starts. The current micro costing approach allows us to record in detail all processes happening at each visit and their purpose (for research or service delivery). The unit cost will then be reported disaggregating research-related costs.

Participant costs

Data are collected through voluntary questionnaires administered to all participants in the PrEP and ITx cohorts at one visit (follow-up at 12 months). In the questionnaires, we collect general information regarding the participant's household, employment and income, out-of-pocket expenditures including transportation fees, consultation fees, non-HIV laboratory tests, non-HIV medication (vitamins, antibiotics and others) and food, any time lost due to PrEP or ITx appointments, including travel time, consultation time and loss of income: the participant's time and that of her family/friends will be ascertained. Family/friends time will be estimated from the proportion of visits where a family member/friend escorted the participant.

Modelling

All modelling exercises will be informed from the data collected during the TAPS study on behaviour, uptake, linkage, retention and medication adherence as well as the costing data. A decision analytic economic modelling approach will be used to look at issues of health system capacity (staff constraints) and equity (poverty analysis using patient-related costs within the cohort). The direct impact on costs and health gains that the introduction of PrEP and ITx might have had on the study cohorts and the service provided in the clinics will be explored.

A population-level transmission model fitted to the South African epidemic will be used, with a special emphasis on transmission within FSW groups with high mobility model focusing on the estimated impact that the introduction of PrEP and ITx might have, should the intervention be scaled up nationally. Population-level data will be gathered from the literature. Outputs of the transmission model will include cost-effectiveness and budget impact measures. A series of scenario analyses might be needed to reflect the different strategies for scale up that policymakers might consider. We will consult all stakeholders (both users and policymakers) during the process of defining the scenarios for scale up to ensure that the most realistic scenarios are tested. We will aim to estimate the reduction in health costs of implementing both interventions. Therefore, we expect savings from infections averted while on PrEP and from less 'other' HIV care if treatment is started early.

ETHICS AND DISSEMINATION

Ethical considerations

As an implementation science research study including human subjects and medication, this study has taken all ethical issues into consideration in line with ICH-GCP (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Good Clinical Practice) guidelines. These include the risks and benefits of taking the study medications as well as the participation in the study itself, the informed consent process, maintaining confidentiality and participation reimbursement. This protocol has been reviewed and approved by the Wits Human Research Ethics Committee (HREC—reference number: 140502) and the Medicines Control Council (MCC—reference number: 20140740), South Africa. The protocol was initially approved by both committees on 8 September 2014, and 15 October 2014 respectively. An amendment was approved subsequently (16 March 2016) following MCC approval of new indication for FTC/TDF and changes in DoH treatment-eligibility criteria.

As this project is not a clinical trial but rather an implementation study, using a product not registered for the relevant indications in South Africa at the time of ethical and MCC applications, the requirements for ethical and MCC approvals were unclear. As with other demonstration projects globally, the project was held to clinical trial standards during the course of the review with questions about procedure, monitoring and participant support throughout the process. In particular, the project is seeking to evaluate the willingness of FSW's to take up and use PrEP and ITx; therefore, we were strongly committed to delivering the interventions in a 'real-world' context which meant excluding reimbursements for clinic visits. This had to be negotiated with the ethics and MCC committees, where a participant fee was suggested, based on the guarantee of minimal invasive procedures (eg, nothing outside of what would be carried out routinely in a public health clinic) and limited waiting time spent in the clinics. In the end, it was agreed that participants would not be paid given the project was offering new interventions for free on top of routine services, but those participants participating in the IDIs would be reimbursed for transport costs at R50.

Owing to the vulnerable nature of this population, confidentiality was an important factor to incorporate into all aspects of the project, but in particular the design of clinical processes. All staff members, whether in contact with participants or not, were trained on how to maintain confidentiality of participants and all patient files, questionnaire data and specimens are being labelled and managed in such a way to safeguard identities.

Dissemination

A stakeholder engagement plan has been implemented as part of the project, which includes the formation of a sex-worker focused community advisory board (CAB), engagement with officials in the South African health sector both at the national and local levels, engagement with partners and stakeholders at the international level, and continuous community outreach and education including sensitisation trainings for community members and Wits RHI staff. The engagement nationally and internationally has included participation on WHO guidelines committees, South African DoH guidelines committees for PrEP and ITx and the new National Sex Worker Plan, as well as plenaries and other presentations at international and local conferences.

The stakeholder engagement plan also includes the dissemination of information about the study as it progresses through the channels mentioned above, as well as eventual dissemination of results. Once the study is completed, study staff will first disseminate results to TAPS participants. This may be carried out through meetings or SMS. Results will be presented to local health officials and stakeholders at meetings, and then sent out through press releases to other partners.

Finally, investigators will publish the main study results as well as findings from the multiple research components of the study, namely the economic evaluation, qualitative research and other clinical and process data. Results from the study will also be presented at various conferences. We will aim to follow STROBE guidelines in the presentation of results; these guidelines were followed in developing the protocol.[41]

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Contributors RE, GBG, WDFV and HR conceived and designed the study. RE, GBG and JM managed the study and data collection. RE, GBG and JM analysed the data. RE, GBG, GA and JM developed materials and analysis tools. RE and GBG wrote the initial draft. RE, GBG, GA, JM, WDFV and HR reviewed the final draft.

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Competing interests GBG, RE, GA and JM declare no competing interests. WDFV has served on Gilead advisory boards; in addition, he is designing a study that requests a donation of a Gilead product. HR was the protocol chair of a microbicide trial involving a Gilead product and has been and is the principal investigator for several trials involving study drug donations from Gilead.

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